

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Jeayuh Lin Examiner #: 77403 Date: 11/20/03
 Art Unit: 3065990 Serial Number: 09/706584
 Mail Box and Bldg/Room Location: CP2 4601 Results Format Preferred (circle) PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Method and devices for heart treatment
 Inventors (please provide full names): Richard L. Madler; U. Hiram Chee

Earliest Priority Filing Date: 11/5/99

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Search for method of treating ischemia

- imaging heart -> Finding
 - Source of oxygenated ^{blood} source
 - Area with underperfused region
 - Various modality
 - Tissue between oxygenated source & underperfused region
- Introduce stimulus to promote angiogenesis (blood vessel ^{capillary} growth)
 - from oxygenated blood source - underperfused region
 - Injury, growth factor, protein
- Sustaining blood supply i.e. injury by piercing, heating, etc.
 - Exercise

demand for

STAFF USE ONLY

Searcher: J Sim
 Searcher Phone #: 308-4836
 Searcher Location: ELC 3700
 Date Searcher Picked Up: _____
 Date Completed: 11/28/03
 Searcher Prep & Review Time: _____
 Clerical Prep Time: _____
 Online Time: _____

Type of Search

NA Sequence (#) _____
 AA Sequence (#) _____
 Structure (#) _____
 Bibliographic _____
 Litigation _____
 Fulltext _____
 Patent Family _____
 Other _____

Vendors and cost where applicable

STN ☒ _____
 Dialog ☒ _____
 Questel/Orbit _____
 Dr. Link _____
 Lexis/Nexis _____
 Sequence Systems _____
 WWW/Internet _____
 Other (specify) _____

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 144

Therapeutic angiogenesis in critical limb and myocardial ischemia

...in animal models of ischemia has shown that administration of angiogenic growth factors, either as a recombinant protein or by gene transfer, can augment nutrient **perfusion** through neovascularization to **promote** the development of supplemental collateral blood vessels that will constitute endogenous bypass conduits around occluded native arteries; a strategy termed "therapeutic **angiogenesis**". In animal models and clinical trials, the best studied cytokines with angiogenic activity are vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF). Clinical trials of therapeutic **angiogenesis** in patients with critical limb ischemia demonstrated resolution of rest pain and/or improved limb integrity, increased pain-free walking time and ankle-brachial index...

...magnetic resonance imaging. Initial clinical trials in patients with end-stage coronary artery disease using direct myocardial injection via thoracotomy resulted in large increases in **exercise** time and marked reductions in anginal symptoms, as well as objective evidence of improved **perfusion** and left ventricular function. Larger scale placebo-controlled trials have been limited to intracoronary and intravenous administration of recombinant protein, and have not shown significant improvement in **exercise** time or angina compared to placebo. Larger scale placebo-controlled studies of gene transfer using catheter-based endocardial delivery are in progress. Future clinical studies...

...administration, and combinations of growth factors, as well as the requirement for endothelial progenitor cell or stem cell supplementation, to provide effective and safe therapeutic **angiogenesis** for patients with critical limb ischemia and chronic myocardial ischemia who are not candidates for conventional revascularization procedures.

MEDICAL DESCRIPTORS:

...*limb ischemia--therapy--th; *heart muscle ischemia--diagnosis--di; *heart muscle ischemia--drug therapy--dt; *heart muscle ischemia--etiology--et; *heart muscle ischemia--therapy--th; * **angiogenesis** ; *endothelium cell; *cell proliferation; *smooth muscle fiber; *hypotension--side effect--si; *edema--side effect--si; *anemia--side effect--si; *thrombocytopenia--side effect--si

11/3,KWIC/10 (Item 1 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

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15738501 22979588 PMID: 14615023

Angiogenic gene therapy with adenovirus 5 fibroblast growth factor-4 (Ad5FGF-4): a new option for the treatment of coronary artery disease.

Grines Cindy; Rubanyi Gabor M; Kleiman Neal S; Marrott Pran; Watkins Matthew W

William Beaumont Hospital, Royal Oak, Michigan 48073, USA.
cgrines@beumont.edu

American journal of cardiology (United States) Nov 7 2003, 92 (9B)

p24N-31N, ISSN 0002-9149 Journal Code: 0207277

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: In Process

16/3,KWIC/1 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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12006994 Genuine Article#: 720FC No. References: 17

Title: Vascular endothelial growth factor mRNA expression and arteriovenous balance in response to prolonged, submaximal exercise in humans

Author(s): Hiscock N; Fischer CP; Pilegaard H; Pedersen BK (REPRINT)
Corporate Source: Rigshosp, Dept Infect Dis, Copenhagen Muscle Res Ctr, Dpt 7641, Blegdamsvej 9/DK-2100 Copenhagen//Denmark/ (REPRINT);
Rigshosp, Dept Infect Dis, Copenhagen Muscle Res Ctr, Dpt 7641, DK-2100 Copenhagen//Denmark/; Univ Copenhagen, August Krogh Inst, DK-2100 Copenhagen//Denmark/

Journal: AMERICAN JOURNAL OF PHYSIOLOGY-HEART AND CIRCULATORY PHYSIOLOGY, 2003, V285, N4 (OCT), PH1759-H1763

ISSN: 0363-6135 Publication date: 20031000

Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA

Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

Title: Vascular endothelial growth factor mRNA expression and arteriovenous balance in response to prolonged, submaximal exercise in humans

Abstract: Angiogenesis, the **growth** of new **blood vessels** from existing ones, occurs in the skeletal muscle as an adaptive response to **exercise** that satisfies the increased requirement of this tissue for oxygen delivery and metabolic processes. Of the factors that have been identified to regulate this process...

...to measure the skeletal muscle VEGF mRNA content and arteriovenous protein balance across the working leg in response to a single bout of prolonged, submaximal **exercise**. Seven physically active males completed 3 h of two-legged kicking ergometry. Muscle biopsies were collected from the vastus lateralis muscle from both working legs, and blood samples were collected from one femoral artery and femoral vein before, during, and in recovery from **exercise**. We show that the **exercise** stimulus elicited a decrease in VEGF protein arteriovenous balance across the **exercising** leg ($P = 0.007$), and a ninefold elevation in skeletal muscle VEGF mRNA expression ($P < 0.001$). The changes in VEGF protein balance and mRNA content were most pronounced 1 h after the cessation of **exercise**. In conclusion, these findings demonstrate that submaximal **exercise**, suitable for humans with low CV fitness, induces a decrease in VEGF arteriovenous balance that is likely to be of clinical significance in **promoting** angiogenic effects.

16/3,KWIC/2 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

04470799 Genuine Article#: TF258 No. References: 32

Title: VEGF GENE-EXPRESSION IS UP-REGULATED IN ELECTRICALLY STIMULATED RAT SKELETAL-MUSCLE

Author(s): HANG J; KONG L; GU JW; ADAIR TH
Corporate Source: UNIV MISSISSIPPI, MED CTR, DEPT PHYSIOL & BIOPHYS, 2500 N STATE ST/JACKSON//MS/39216; UNIV MISSISSIPPI, MED CTR, DEPT PHYSIOL & BIOPHYS/JACKSON//MS/39216; UNIV MISSISSIPPI, MED CTR, DEPT MICROBIOL/JACKSON//MS/39216

Journal: AMERICAN JOURNAL OF PHYSIOLOGY-HEART AND CIRCULATORY PHYSIOLOGY, 1995, V38, N5 (NOV), PH1827-H1831

ISSN: 0363-6135

Language: ENGLISH Document Type: NOTE (Abstract Available)

...Abstract: purpose of this study was to determine whether VEGF gene expression is upregulated in chronically stimulated skeletal muscles, where hypoxia is thought to trigger the **growth** of **blood vessels**. The right anterior tibialis and extensor digitorum longus muscles of 12 rats were stimulated electrically (10 Hz, 300 μ s pulses) for up to 21 ...

...are consistent with a metabolic hypothesis in which tissue oxygenation controls VEGF expression. These studies support the hypothesis that VEGF has a physiological role in **promoting** angiogenesis in stimulated skeletal muscle.

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19/3,KWIC/1 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

10367485 Genuine Article#: 518HF No. References: 26

Title: Therapeutic angiogenesis for critical limb ischemia: invited commentary

Author(s): Messina LM (REPRINT) ; Brevetti LS; Chang DS; Paek R; Sarkar R
Corporate Source: Univ Calif San Francisco M488,Dept Surg, Div Vasc
Surg,505 Parnassus Ave/San Francisco//CA/94143 (REPRINT); Univ Calif
San Francisco M488,Dept Surg, Div Vasc Surg,San Francisco//CA/94143
Journal: JOURNAL OF CONTROLLED RELEASE, 2002, V78, N1-3 (JAN 17), P285-294
ISSN: 0168-3659 Publication date: 20020117
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

Title: Therapeutic angiogenesis for critical limb ischemia: invited commentary

...Abstract: occlusive disease results in tissue ischemia of the legs and is relatively common in the elderly. Clinically, it may be asymptomatic, cause muscle pain during **exercise**, or progress to a severe degree of ischemia that may result in limb loss. Although bypass surgery, and angioplasty have increased the rate of limb salvage in these patients, amputation of the affected limb remains a common outcome for many patients. Therapeutic **angiogenesis** is the administration of angiogenic factors, or genes encoding these factors, to **promote** neovascularization and thereby increase blood flow to the ischemic leg. We have developed an animal model of hindlimb ischemia in which to study therapeutic **angiogenesis**. We chose nitric oxide as the angiogenic factor for our experiments because of its ability to induce **angiogenesis**, vasodilation, and inhibit inflammation. In this review, we will discuss our experience with our model of hindlimb ischemia, as well as discuss our results of gene therapy for therapeutic **angiogenesis** using nitric oxide. (C) 2002 Published by Elsevier Science B.V.

...Identifiers--ENDOTHELIAL GROWTH-FACTOR; INTRAMUSCULAR GENE-TRANSFER; BLOOD-FLOW; RABBIT MODEL; IN-VIVO; RAT; HINDLIMB; PROLIFERATION; EXPRESSION; **PERFUSION**

19/3,KWIC/2 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

07906752 Genuine Article#: 222HV No. References: 23

Title: Heparin potentiates collateral growth but not growth of intramyocardial endarteries in dogs with repeated coronary occlusion

Author(s): Fujita M (REPRINT) ; Kihara Y; Hasegawa K; Nohara R; Sasayama S
Corporate Source: KYOTO UNIV,COLL MED TECHNOL, SAKYO KU, 53
KAWAHARACHO/KYOTO 606//JAPAN/ (REPRINT); KYOTO UNIV,DEPT CARDIOVASC
MED, GRAD SCH MED/KYOTO 606//JAPAN/
Journal: INTERNATIONAL JOURNAL OF CARDIOLOGY, 1999, V70, N2 (JUL 31), P
165-170
ISSN: 0167-5273 Publication date: 19990731
Publisher: ELSEVIER SCI IRELAND LTD, CUSTOMER RELATIONS MANAGER, BAY 15,
SHANNON INDUSTRIAL ESTATE CO, CLARE, IRELAND
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

...Abstract: beneficial effect of heparin on canine collateral development.
Seventeen adult mongrel dogs were instrumented for measurements of a

subendocardial segment length in the central area **perfused** by the left circumflex coronary artery, its flow, and left ventricular pressure. A pulsed Doppler flow probe and an externally inflatable pneumatic occluder were placed...

...neovascularization toward the ischemic area) was comparable in dogs with and without heparin (15.4+/-12.4% vs. 21.1+/-13.6%, p=NS). Heparin **promotes** nonsprouting **angiogenesis** (arteriogenesis) of preformed collateral vessels but not neovascularization toward the ischemic area in dogs with brief repetitive coronary occlusions. (C) 1999 Elsevier Science Ireland Ltd...

...Identifiers--REGIONAL MYOCARDIAL-FUNCTION; MOLECULAR-WEIGHT HEPARIN; STABLE-EFFORT ANGINA; TREADMILL CAPACITY; CONSCIOUS DOGS; ARTERY DISEASE; CANINE MODEL; DOUBLE-BLIND; **EXERCISE**; PRETREATMENT

19/3,KWIC/3 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

05709623 Genuine Article#: WR446 No. References: 15
Title: Effect of basic fibroblast growth factor on myocardial angiogenesis in dogs with mature collateral vessels
Author(s): Shou M; Thirumurti V; Rajanayagam S; Lazarous DF; Hodge E; Stiber JA; Pettiford M; Elliott E; Shah SM; Unger EF (REPRINT)
Corporate Source: NHLBI,PHYSL & PHARMACOL SECT, CARDIOL BRANCH, NIH, BLDG 10, ROOM 7B15, 10 CTR DR /BETHESDA//MD/20892 (REPRINT); NHLBI,PHYSL & PHARMACOL SECT, CARDIOL BRANCH, NIH/BETHESDA//MD/20892
Journal: JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, 1997, V29, N5 (APR), P1102-1106
ISSN: 0735-1097 Publication date: 19970400
Publisher: ELSEVIER SCIENCE INC, 655 AVENUE OF THE AMERICAS, NEW YORK, NY 10010
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

Title: Effect of basic fibroblast growth factor on myocardial angiogenesis in dogs with mature collateral vessels

Abstract: Objectives. We sought to evaluate the potential of basic fibroblast growth factor (bFGF) to enhance coronary collateral **perfusion** in dogs with chronic single-vessel coronary occlusion. A secondary goal was to examine whether the salutary effects of bFGF treatment, previously proved effective in...

...bFGF, an angiogenic growth factor, is currently the subject of a Phase I trial in patients with ischemic heart disease. It has been shown to **promote** collateral development in dogs with progressive coronary occlusion when given during the period of natural collateralization. The effect of bFGF on quiescent collateral vessels, a...

...circumflex coronary artery and randomized to bFGF (1.74 mg/day for 7 days), a regimen previously proved effective, or to saline solution. Maximal collateral **perfusion** was assessed 6 months later, and the dogs were reassigned to a course of bFGF or saline solution. Collateral **perfusion** was reevaluated after the second treatment course.

Results. At 6 months, collateral function was identical in the groups treated initially with bFGF and saline solution...

...Identifiers--BLOOD-FLOW MEASUREMENTS; CORONARY-ARTERY; HEPARIN; **EXERCISE**

Research Fronts: 95-2892 001 (VASCULAR ENDOTHELIAL GROWTH-FACTOR; TUMOR **ANGIOGENESIS** ; COORDINATE EXPRESSION)

95-3557 001 (CEREBRAL BLOOD-FLOW DURING CARDIOPULMONARY BYPASS;
REGIONAL VASCULAR RESERVE; FETAL SHEEP; MYOCARDIAL HEMATOCRIT GRADIENT;
DIABETIC RATS)

19/3,KWIC/4 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
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05909883 EMBASE No: 1994315785

Clinical significance of coronary vascular adaptations to exercise training

McKirnan M.D.; Bloor C.M.
Department of Pathology, UCSD School of Medicine, 9500 Gilman Drive, San
Diego, CA 92093-0612 United States
Medicine and Science in Sports and Exercise (MED. SCI. SPORTS EXERC.) (United States) 1994, 26/10 (1262-1268)
CODEN: MSCSB ISSN: 0195-9131
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Clinical significance of coronary vascular adaptations to exercise training

Coronary vascular adaptations to **exercise** training have been extensively studied at the microscopic level in animals and correlated with direct and indirect measurements of myocardial blood flow in patients with coronary artery disease. Animals have permitted more extensive study. These findings have generally supported an increased blood flow to the myocardium with **exercise** training. However, consistent positive structural and functional adaptations to training have not been observed in large animals. Clinical studies have been limited by methodological problems related to techniques for detecting ischemia and measuring myocardial blood flow and the variability in **exercise** stimulus. Well-established ischemia and high-intensity, long-duration training were the factors that **promoted** vascular growth in **exercising** patients with coronary artery disease. Animals studies also have demonstrated the necessity for myocardial ischemia to be present to induce coronary collateral development with **exercise** training. Optimal **promoters** of vascular growth in patients with coronary disease may consist of pharmacological interventions combined with **exercise** training.

MEDICAL DESCRIPTORS:

*coronary artery blood flow; *coronary artery collateral circulation; ***exercise**
adaptation; **angiogenesis** ; conference paper; heart muscle **perfusion** ;
human; nonhuman

19/3,KWIC/5 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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09468014 21241646 PMID: 11345391

Transendocardial delivery of autologous bone marrow enhances collateral perfusion and regional function in pigs with chronic experimental myocardial ischemia.

Fuchs S; Baffour R; Zhou Y F; Shou M; Pierre A; Tio F O; Weissman N J;
Leon M B; Epstein S E; Kornowski R
Cardiovascular Research Institute, Washington Hospital Center,
Washington, DC 20010, USA. sxf6@mhg.edu

Journal of the American College of Cardiology (United States) May 2001,
37 (6) p1726-32, ISSN 0735-1097 Journal Code: 8301365
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Transendocardial delivery of autologous bone marrow enhances collateral perfusion and regional function in pigs with chronic experimental myocardial ischemia.

OBJECTIVES: We tested the hypothesis that intramyocardial injection of autologous bone marrow (ABM) **promotes** collateral development in ischemic porcine myocardium. We also defined, in vitro, whether bone marrow (BM) cells secrete vascular endothelial growth factor (VEGF) and macrophage chemoattractant...

... MCP-1). **BACKGROUND:** The natural processes leading to collateral development are extremely complex, requiring multiple growth factors interacting in concert and in sequence. Because optimal **angiogenesis** may, therefore, require multiple angiogenic factors, we thought that injection of BM, which contains cells that secrete numerous angiogenic factors, might provide optimal therapeutic **angiogenesis**. **METHODS:** Bone marrow was cultured four weeks in vitro. Conditioned medium was assayed for VEGF and MCP-1 and was added to cultured pig aortic...

... n = 7) was injected transendocardially into the ischemic zone (0.2 ml/injection at 12 sites). Echocardiography to assess myocardial thickening and microspheres to assess **perfusion** were performed at rest and during stress. **RESULTS:** Vascular endothelial growth factor and MCP-1 concentrations increased in a time-related manner. The conditioned medium ...

... 37 +/- 56 during pacing, p = 0.23). **CONCLUSIONS:** Bone marrow cells secrete angiogenic factors that induce endothelial cell proliferation and, when injected transendocardially, augment collateral **perfusion** and myocardial function in ischemic myocardium.

; Bone Marrow Transplantation--instrumentation--IS; Cells, Cultured; Chronic Disease; Echocardiography; Endothelial Growth Factors; **Exercise** Test; Feasibility Studies; Injections--instrumentation--IS; Injections--methods--MT; Lymphokines; Monocyte Chemoattractant Protein-1; Myocardial Ischemia--pathology--PA; Myocardial Ischemia--physiopathology--PP; Myocardial Ischemia--ultrasonography...

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JLin

FILE 'HCAPLUS, LIFESCI, MEDICONF, RUSSCI' ENTERED AT 10:18:02 ON 28 NOV
2003

L1 73491 S ISCHEMI?
L2 379382 S CARDIAC? OR MYOCARD? OR HEART?
L3 135404 S OXYGENAT? OR PERFUS? OR UNDERPERFUS?
L4 153098 S IMAGING?
L5 249864 S SPECT OR ((SINGLE() PHOTON() EMISSION() COMPUTED) OR (POSITRON()
L6 237 S ECHOPLANAR? OR ECHO() PLANAR?
L7 236 S L1 AND (L2 AND L3) AND L4
L8 94 S L5 AND L7
L9 1 S L6 AND L7
L10 22399 S ANGIOGENES?
L11 9 S (L8 OR L9) AND L10
L12 200407 S GROWTH() FACTOR? OR RECOMBINANT() PROTEIN?
L13 1008607 S STIMULAT? OR IRRITAT? OR INJUR?
L14 2993 S L10 AND L12 AND L13
L15 3 S L1 AND L2 AND (L4 OR L5) AND L14
L16 12 S L11 OR L15
L17 11 DUP REMOVE L16 (1 DUPLICATE REMOVED)

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Set	Items	Description
S1	93	AU='MUELLER R L'
S2	14	AU='MUELLER RICHARD L'
S3	107	S1 OR S2
S4	38	AU='CHEE U':AU='CHEE URIEL HIRAM'
S5	5	S3 AND S4
S6	4051	(CARDIAC OR HEART) (S) ISCHEM?
S7	1146862	IMAG?
S8	12030	OXYGENAT? OR PERFUS? OR UNDERPERFUS? OR UNDER() PERFUS
S9	11	UNDER() PERFUS?
S10	12030	S8 OR S9
S11	4501	ANGIOGENES?
S12	147	S6 AND S7
S13	104	S10 AND S11
S14	5	S12 AND S13
S15	10	S5 OR S14

? show files

File 347:JAPIO Oct 1976-2003/Jul(Updated 031105)
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File 350:Derwent WPIX 1963-2003/UD,UM &UP=200376
(c) 2003 Thomson Derwent

File 371:French Patents 1961-2002/BOPI 200209
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Set	Items	Description
S1	89466	ANGIOGENES?
S2	1104731	PROMOT?
S3	3012	S2(3N)S1
S4	529593	EXERCIS?
S5	11	S3(S)S4
S6	493982	PERFUS?
S7	14373	S4(S)S6
S8	115	S1 AND S7
S9	16	S2 AND S8
S10	23	S5 OR S9
S11	10	RD (unique items)
S12	4314	BLOOD(3N)VESSEL?(3N)GROWTH?
S13	384	S2(S)S12
S14	4	S4 AND S13
S15	4	S14 NOT S10
S16	2	RD (unique items)
S17	22	(S1 OR S12) AND S2 AND S4 AND S6
S18	5	S17 NOT (S10 OR S14)
S19	5	RD (unique items)

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File 2:INSPEC 1969-2003/Nov W3
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File 34:SciSearch(R) Cited Ref Sci 1990-2003/Nov W4
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File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec
(c) 1998 Inst for Sci Info

File 73:EMBASE 1974-2003/Nov W4
(c) 2003 Elsevier Science B.V.

File 155:MEDLINE(R) 1966-2003/Nov W4
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Set	Items	Description
S1	2895211	CARDIAC? OR MYOCARD? OR HEART?
S2	663398	ISCHEMI?
S3	1805975	IMAGING? OR SPECT OR SINGLE()PHOTON()EMISSION()COMPUTED()T- OMOGRAPH? OR POSITRON()EMISSION()TOMOGRAPH? OR PET OR MAGNETI- C()RESONANCE OR MRI
S4	12655	(ECHOPLANAR OR ECHO()PLANAR OR MYOCARDIAL()PERFUSION)()IMA- GING
S5	1805975	S3 OR S4
S6	295911	S1(S)S2
S7	24207	S5 AND S6
S8	89360	ANGIOGENES?
S9	3954002	STIMULAT? OR IRRITAT? OR INJUR?
S10	852878	GROWTH()FACTOR? OR RECOMBINANT()PROTEIN?
S11	609317	OXYGENAT? OR PERFUS?
S12	17916	S8 AND S9
S13	49	S7 AND S12
S14	33	S13 AND S10
S15	21	S13 AND S11
S16	38	S14:S15
S17	26	RD (unique items)
S18	49	S13
S19	29	RD (unique items)
S20	10	S19 AND PY<2000

? show files

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File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec
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File 73:EMBASE 1974-2003/Nov W3
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File 155:MEDLINE(R) 1966-2003/Nov W3
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Case Analysis 09/706,584

Summary

The election requirement paper ~~No. 6 was in error in that it proposed~~ subcombinations as species and failed to require election of the bona fide method species present - alternative sustained mechanical injury device usages and alternative cell growth factor delivery vehicle usage.

*No
right should
have been done*

The Office First Action paper No. 12 is in error in that the base reference Hammond is not anticipatory since it does not even partly reveal either identifying the target bridging area or the sustained demand steps a), c) of applicants angiogenic treatment method.

The Office first Action paper No. 12 is further in error in that the Mann in view of Pearlman rejection under 35USC103 is also improper.

The Mann reference is fairly characterizable as recognizing that both mechanical injury and cell-growth factor injection may be used synergistically to promote angiogenesis in ischemic myocardium.

Otherwise Mann is similarly deficient to Hammond re steps a) and c) Pearlman, which is used to track re-perfusion at a treated myocardial site, does not supplant these teaching deficiencies in combination therewith.

*Hammond
Mann +
Pearlman
no good
Mann
Injury /
growth - Promote
angio*

The Examiner is misunderstanding the invention in this regard. It would be helpful for him to work closely with a mentor to read each claim limitation in light of the specification against the prior art and resist the tendency to dilute the literal claim language with a compromise reading in relation to cited art.

The Invention

The invention pertains to angiogenic treatment of heart ischemia where angiogenesis or the growth of new myocardial blood vessels may be induced either by angiogenic drug delivery ('drug trigger') and/or by an injury stimulus caused by delivery of an injury agent (drug or energy, termed a 'biological trigger'). First cardiac imaging is used to identify an underperfused region of the heart which is at risk is identified. Then a nearby small-vessel blood supply capable of providing perfusing blood is identified. Finally, the bridging region between this available blood source

*- Imagin
ID. blood
- supply
- bridge
Blood source*

and the underperfused area is treated with the angiogenic drug and/or with the prior delivery of an injury stimulus agent to deliberately create an injury or 'capillary blush' in the bridging region in order to induce blood delivery to the underperfused region. Once such an induction is made, "sustained demand" is used to make permanent the additional bloodflow channels so-induced, meaning that chemical or viral agents or an exercise regimen or repeat of the injury agent biological trigger is adhered to such that the augmented flow pattern is made permanent by the body. (Specification page 12 -13 bridging summarizes this.)

Formalities

Serial no. Provided spec page 14 line 2 is incorrect. Should be corrected and status updated.

The Initial Election Requirement

In consideration of the above description the species election requirement paper No. 6 was incorrect.

"Species I" - The heart exercising device of Fig. 17 is a cardiometer which has no species alternative to itself under the disclosure, moreover exercise is not mutually exclusive under the disclosure to the other sustained demand devices, since exercise is stated to be practiced along with sustained mechanical injury as an oxygen demand promoter(specification page 26 lines 12-16).

"Species II" - Alternative species of mechanical injury device are present and represented in the claims however a proper species election statement would announce them: --Species of alternative coring devices (as represented by Figs. 5A and 7A through 9B) themselves alternative to the differing wire injury devices (Fig. 5B and 10 - 13) themselves alternative to the different endocardial scuffing device(s) (Figs., 14 - 15). Since their selection in a given patient is specific to the site of ischemia (deep wall or surface) their usage is mutually exclusive to each other.--

"Species III" - Since both cardiac cell-growth factor stimuli and mechanical

devices are used to both stimulate and sustain angiogenesis, alone or in use together, they are not alternative to each other. Since the growth cell factors (FGF-2, FGF-1, VEGF, PDGF, IDGF-1) are stated to be usable together in combination they are not mutually exclusive under the disclosure and therefore not species, see spec page 4 lines 22 - 26. What is alternative is the installment technique by recombinant protein or vector intermediate or whole cell (myoblast) delivery vehicle. Since viral transfection (page 6 line 8) is akin to recombinant protein delivery, again it appears that cell growth factors are usable together and both as angiogenic stimuli and sustainers, and only -- Species of alternative growth factor delivery vehicles are present as represented by claims 6, 7 and 8...-- may be posed to the applicants.

“Species IV” - An angiogram pertains to x-ray fluoroscopic imaging of the condition of the heart's arteries and therefore is not the right nomenclature for the alternatives recited in the specification pages 4 lines 9 - 13 and page 11 lines 3 - 14 which both use the conventional angiogram definition. Alternative modalities of heart imaging including myocardial perfusion imaging are indeed present (MPI, SPECT, PET, ultrasound, x-ray, MRI, thallium scintigraphy) however they may be used together and therefore are not alternative, specification page 11 line 10. Additionally, the sole claim directed to these, claim 2 is in a Markush-type format and the ‘unduly burdensome’ requirement of MPEP 808.01(a) where claims are generic to the species feature being elected is unmet.

The net effect now is that we are dealing with method steps to some subcombinations (cell-growth delivery stimulus steps and sustained demand exercising steps) and leaving out other subcombinations (mechanical stimulus step types -claims 10-16) and further step of second stimulus stage +imaging-claim 17) as well as omitting one of two proper species election options (Species III above as pertains to claims 6-8).

The Claim Rejections

Base claim 1 calls for 1) initial imaging to identify an available blood vessel(s) source, an underperfused ischemic areaa and a bridging therapeutic target area across which angiogenesis must be stimulated, 2) introduction of the angiogenic stimulus at plural sites within the target area, and 3) sustainment of the oxygen demand at the target area for a time sufficient to convert the created capillary network to an arterial network.

It is important to understand the three categories of cardiac muscle to which applicants refer:

Normal - well-perfused and viable

Hibernating - Specification page 9 lines 20-29; muscle which is functionally dormant but yet viable. Aslo termed ischemic/underperfused

Infarcted - No longer viable

The term 'hibernating' is well-likenable to the natural case from which the word is drawn because under chronic ischemic conditions portions of myocardium go into an under-performing sleep state identified by electrical responsiveness but kinetic sluggishness and causing effort angina, however the muscle is revivable once re-perfused.

Hence while claim 1 step b) is likenable to 'wakening the bear in mid-winter', step c) pertains to 'putting the bear on a treadmill or poking him for a sustained period so he stays awake'. Specifically, sustained oxygen demand must be caused in the treated tissue to an extent and long enough to stimulate a transition from initial generation of capillary passageways in the (disordered) myocardial sinusoids to permanent small-artery structure.

Hammond does not in any way describe this latter step c). Anticipation is predicated upon certainty where inherency is invoked; the Examiner cannot simplify the rejection burden by invoking 'inherency' to bridge an untaught teaching gap.

Hammond in fact does not teach step a) either. Since Hammond is attempting 1) direct coronary infusion (i.e at best an injection into a vessel 'proximate to a boundary of the under-perfused region') or 2) direct infusion to the under-perfused site, Hammond has no need to identify a target bridging area and therefore is not tailored to effect re-perfusion in

the bridging area but rather to cause wholesale angiogenesis by saturation infusion as per 1) or hibernation site angiogenesis by direct access puncture as per 2).

Hammond is not an anticipatory teaching.

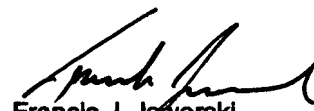
103 Mann v Pearlman

The Mann reference exhibits the artisan's cognizance that both mechanical injury and cell growth factor infusion can act synergistically to promote angiogenesis. However Mann is similarly limited re steps a) and c) to Hammond...there is no teaching of these steps. Pearlman merely established that angiogenic re-perfusion of myocardium however promoted can be monitored via a particular MRI imaging technique and therefore does not remedy the deficiencies of Mann.

Mann v. Pearlman is not a sustainable rejection ground.

Patentability findings - Exercise has long been known to promote collateral circulation within the myocardium. It is probably a STIC search topic since for this feature standing alone (the proposal that exercise would stimulate growth of artificially induced blood vessels analogous to the way it stimulates growth of the natural myocardial vessels) would not necessarily develop through the patent literature. *STIC* *Stark*

10d


Francis J. Jaworski
Primary Examiner

7-1-03

5/3/4 (Item 4 from file: 350)
DIALOG(R)File 350:Derwent WPIX
(c) 2003 Thomson Derwent. All rts. reserv.

013859173 **Image available**

WPI Acc No: 2001-343386/200136

XRPX Acc No: N01-248684

**Treatment method for patient with heart disorders, involves creating
annulus of injury about core of healthy cells in myocardial layer of
heart between underperfused region and source of oxygenated blood**

Patent Assignee: MICROHEART INC (MICR-N); SCIMED LIFE SYSTEMS INC (SCIM-N)

Inventor: CHEE U H ; MUELLER R L

Number of Countries: 030 Number of Patents: 006

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
WO 200132088	A2	20010510	WO 2000US41905	A	20001103	200136 B
AU 200136424	A	20010514	AU 200136424	A	20001103	200149
EP 1229845	A2	20020814	EP 2000991944	A	20001103	200261
			WO 2000US41905	A	20001103	
US 6524324	B1	20030225	US 99163704	P	19991105	200323
			US 2000706016	A	20001103	
JP 2003512884	W	20030408	WO 2000US41905	A	20001103	200333
			JP 2001534300	A	20001103	
US 20030114872	A1	20030619	US 99163704	P	19991105	200341
			US 2000706016	A	20001103	
			US 2002304025	A	20021125	

Priority Applications (No Type Date): US 99163704 P 19991105; US 2000706016
A 20001103; US 2002304025 A 20021125

Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
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WO 200132088	A2	E	43	A61B-017/34	
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Designated States (National): AU CA JP

Designated States (Regional): AT BE CH CY DE DK ES FI FR GB GR IE IT LU
MC NL PT SE TR

AU 200136424	A			A61B-017/34	Based on patent WO 200132088
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EP 1229845	A2	E		A61B-017/34	Based on patent WO 200132088
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Designated States (Regional): AL AT BE CH CY DE DK ES FI FR GB GR IE IT
LI LT LU LV MC MK NL PT RO SE SI TR

US 6524324	B1			A61B-017/34	Provisional application US 99163704
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JP 2003512884	W		64	A61B-017/00	Based on patent WO 200132088
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US 20030114872	A1			A61B-017/32	Provisional application US 99163704
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Div ex application US 2000706016

Div ex patent US 6524324



STIC Search Report

EIC 3700

STIC Database Tracking Number: 108741

TO: Jeoyuh Lin
Location: cp2 4c08
Art Unit: 3737
Friday, November 28, 2003

Case Serial Number: 09/706584

From: John Sims
Location: EIC 3700
CP2, 2C08
Phone: 308-4836

john.sims@uspto.gov

Search Notes

Please examine your results carefully. This search employed a large number of search terms, so the results may or may not be on point.

14/3,KWIC/3 (Item 3 from file: 350)
DIALOG(R)File 350:Derwent WPIX
(c) 2003 Thomson Derwent. All rts. reserv.

015051429

WPI Acc No: 2003-111945/200310

Related WPI Acc No: 1996-412586; 1998-610127; 1999-527341; 2001-316488

XRAM Acc No: C03-028637

Increasing contractile function in the heart of a patient, useful for treating heart diseases such as cardiovascular diseases, comprises delivering a transgene encoding an angiogenic protein or peptide to at least one coronary artery

Patent Assignee: DILLMANN W (DILL-I); GIORDANO F J (GIOR-I); HAMMOND H K (HAMM-I); UNIV CALIFORNIA (REGC)

Inventor: DILLMANN W; GIORDANO F J; HAMMOND H K

Number of Countries: 100 Number of Patents: 002

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
WO 200289856	A1	20021114	WO 2002US13990	A	20020503	200310 B
US 20030148968	A1	20030807	US 95396207	A	19950228	200358
			US 95485472	A	19950607	
			US 97852779	A	19970507	
			US 97722271	A	19971229	
			US 9821773	A	19980211	
			US 9868102	A	19980430	
			US 98132167	A	19980810	
			WO 99US2702	A	19990209	
			US 99435156	A	19991105	
			US 2000609080	A	20000630	
			WO 2000US30345	A	20001103	
			US 2001847936	A	20010503	

Priority Applications (No Type Date): US 2001847936 A 20010503; US 95396207 A 19950228; US 95485472 A 19950607; US 97852779 A 19970507; US 97722271 A 19971229; US 9821773 A 19980211; US 9868102 A 19980430; US 98132167 A 19980810; WO 99US2702 A 19990209; US 99435156 A 19991105; US 2000609080 A 20000630; WO 2000US30345 A 20001103

Patent Details:

Patent No Kind Lan Pg Main IPC Filing Notes

WO 200289856 A1 E 129 A61K-048/00

Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW

US 20030148968 A1 A61K-048/00 CIP of application US 95396207
CIP of application US 95485472
Cont of application US 97852779
CIP of application US 97722271
CIP of application US 9821773
CIP of application US 9868102
Cont of application US 98132167
CIP of application WO 99US2702
CIP of application US 99435156
CIP of application US 2000609080
CIP of application WO 2000US30345
CIP of patent US 5792453
CIP of patent US 6100242
Cont of patent US 6174871

Abstract (Basic):

... the power 11 viral particles of recombinant adenovirus was delivered by slow injection into both left and right coronary arteries. Two-dimensional and M-mode **images** were obtained from a right parasternal approach at the papillary muscle level. Studies were performed 1 day before gene transfer and repeated 14 days later...
...The method is useful for treating **heart** diseases including cardiovascular diseases, peripheral vascular diseases, congestive **heart** failure, dilated cardiomyopathy, dilated cardiomyopathy. The method is also useful for increasing blood flow in an **ischemic** tissue of a patient, for increasing contractile function on the **heart** of the patient, and for preventing or alleviating deleterious ventricular remodeling in a patient who has suffered a myocardial infarction...

Technology Focus:

... The vector may also be introduced by injection from a catheter conducted at least 1 cm into the lumen of the arteries, or by retrograde **perfusion** from a catheter placed into a conduit receiving blood from the myocardium. The vector is introduced into a saphenous vein graft and/or an internal...
...an insulin-like growth factor, a hypoxia-inducible factor and an angiogenic polypeptide regulator. The angiogenic protein or peptide stimulates collateral vessel development in the **heart**, thus enhancing blood flow in the **heart**. The vector further comprises a transgene encoding a **cardiac** enhancing protein or peptide, which is a beta-adrenergic signaling protein or peptide (beta-ASP), and which induces the growth or function of myocytes, thus enhancing contractile function in the **heart**. Delivery of the transgene using the vector is predominantly localized to the **heart**, where the vector predominantly transfects **cardiac** cells. Expression of the transgene occurs predominantly within the myocardium, particularly within **cardiac** myocytes. The percent wall thickening in the **heart** is increased. Introduction of the vector into at least one coronary artery may be performed coincident with or following infusion of the artery with a...
...1 ml/minute for about 3 minutes prior to the injection of the vector. The patient has a cardiovascular disease such as atherosclerosis or myocardial **ischemia**. Blood flow within the **heart** is increased. Increasing blood flow in an **ischemic** tissue of a patient comprises delivering a transgene encoding an angiogenic protein or peptide to an **ischemic** region of the tissue by introducing a vector comprising the transgene to the tissue, where the transgene is expressed in the tissue, and subsequently increase blood flow in the tissue. The patient has cardiovascular disease, particularly peripheral vascular disease. The vector is introduced into the tissue by anterograde **perfusion** from a catheter placed into a conduit delivering blood to the tissue, or by retrograde **perfusion** from a catheter placed into a conduit receiving blood from the tissue. The **ischemic** tissue comprises muscle cells, specifically **cardiac** myocytes, where increasing blood flow within the **ischemic** tissue results in increased contractile function. The conduit delivering blood to the tissue is a coronary artery or a femoral artery. The vector is introduced...
...injecting a solution comprising the vector into skeletal muscle, where the angiogenic protein or peptide causes an increase in blood flow and a decrease in **ischemia** in the tissue. The solution comprises at least about one ml. The angiogenic protein or peptide stimulates collateral vessel development in the **heart**, thus enhancing blood flow in the **heart**.

JLin

CORPORATE SOURCE: Angiogenic GENE Therapy (AGENT-2) Study Group,
Department of Medicine, Section of Cardiology, William
Beaumont Hospital, Royal Oak, MI, USA
SOURCE: Journal of the American College of Cardiology (2003),
42(8), 1339-1347
CODEN: JACCDI; ISSN: 0735-1097
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objectives The primary objective of this study was to determine whether intracoronary administration of the adenoviral gene for fibroblast growth factor (Ad5FGF-4) can improve **myocardial perfusion** compared with placebo. Background Animal studies and observational clin. studies have shown improvement in **perfusion** of the **ischemic myocardium** using genes encoding angiogenic growth factors; however, randomized, double-blind data in humans are lacking. Methods We performed a randomized, double-blind, placebo-controlled trial of intracoronary injection of 1010 adenoviral particles containing a gene encoding fibroblast growth factor (Ad5FGF-4) to determine the effect on **myocardial perfusion**. Fifty-two patients with stable angina and reversible **ischemia** comprising >9% of the left ventricle on adenosine single-photon emission computed tomog. (**SPECT**) **imaging** were randomized to gene therapy (n = 35) or placebo (n = 17). Clin. follow-up was performed, and 51 (98%) patients underwent a second adenosine **SPECT** scan after 8 wk. Results Overall (n = 52), the mean total **perfusion** defect size at baseline was 32.4% of the left ventricle, with 20% reversible **ischemia** and 12.5% scar. At eight weeks, Ad5FGF-4 injection resulted in a significant reduction of **ischemic** defect size (4.2% absolute, 21% relative; p < 0.001) and placebo-treated patients had no improvement (p = 0.32). Although the change in reversible **perfusion** defect size between Ad5FGF-4 and placebo was not significant (4.2% vs. 1.6%, p = 0.14), when a single outlier was excluded a significant difference was observed (4.2% vs. 0.8%, p < 0.05). Ad5FGF-4 was well tolerated and did not result in any permanent adverse sequelae. Conclusions Intracoronary injection of Ad5FGF-4 showed an encouraging trend for improved **myocardial perfusion**; however, further studies of therapeutic **angiogenesis** with Ad5FGF-4 will be necessary.

L17 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2002:481702 HCAPLUS
DOCUMENT NUMBER: 137:197543
TITLE: Medical **imaging** techniques in the evaluation
of strategies for therapeutic **angiogenesis**
AUTHOR(S): Pearlman, Justin D.; Laham, Roger J.; Post, Mark;
Leiner, Tim; Simons, Michael
CORPORATE SOURCE: Departments of Medicine and Radiology,
Dartmouth-Hitchcock Medical Center, Lebanon, NH,
03755, USA
SOURCE: Current Pharmaceutical Design (2002), 8(16), 1467-1496
CODEN: CPDEFP; ISSN: 1381-6128
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Recent advancements in our understanding of the basic biol. of **angiogenesis** have prompted a focus on practical applications, both in cardiovascular disease and in oncol. The focus on practical applications has stimulated development of novel noninvasive tools that

JLin

SOURCE: Journal of Pharmacology and Experimental Therapeutics
(2000), 292(2), 795-802
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental
Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Therapeutic **angiogenesis** is a novel approach to the treatment of **myocardial ischemia** based on the use of proangiogenic growth factors to induce the growth of new blood vessels to supply the **myocardium** at risk. This study was designed to assess the safety and efficacy of a single intrapericardial injection of basic fibroblast growth factor (FGF-2) in a porcine model of chronic **myocardial ischemia**. Yorkshire pigs underwent ameroid placement around the left circumflex coronary artery. At 3 wk, animals were randomized to receive a single intrapericardial injection of either saline (n = 10), 3 mg of heparin (n=9), 3 mg of heparin +30 µg of FGF-2 (n = 10), 200 µg of FGF-2 (n = 10), or 2 mg of FGF-2 (n = 10). Coronary angiog., microsphere flow, **magnetic resonance** functional, and **perfusion imaging** were performed before and 4 wk after treatment, at which time histol. anal. was also performed on 3 animals in each group. In **ischemic** pigs, FGF-2 treatment resulted in significant increases in left-to-left angiog. collaterals and left circumflex coronary artery blood flow. These benefits were accompanied by improvements in **myocardial perfusion** and function in the **ischemic** territory, as well as histol. evidence of increased **myocardial** vascularity without any adverse effects. Not one of these benefits was seen in saline- or heparin-treated **ischemic** animals. A single intrapericardial injection of FGF-2 in a porcine model of chronic **myocardial ischemia** results in functionally significant **myocardial angiogenesis**, without any adverse outcomes. This mode of FGF-2 administration may prove to be a useful therapeutic strategy for the treatment of patients with **ischemic heart** disease.

REFERENCE COUNT: 25. THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1999:750406 HCAPLUS

DOCUMENT NUMBER: 131:347070

TITLE: Local perivascular delivery of basic fibroblast growth factor in patients undergoing coronary bypass surgery: results of a phase I randomized, double-blind, placebo-controlled trial

AUTHOR(S): Laham, Roger J.; Sellke, Frank W.; Edelman, Elazer R.; Pearlman, Justin D.; Ware, J. Anthony; Brown, David L.; Gold, Jeffrey P.; Simons, Michael

CORPORATE SOURCE: Angiogenesis Research Center, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, MA, 02215, USA

SOURCE: Circulation (1999), 100(18), 1865-1871

CODEN: CIRCAZ; ISSN: 0009-7322

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Angiogenesis** is a promising treatment strategy for patients who are not candidates for standard revascularization, because it promotes the growth of new blood vessels in **ischemic myocardium**. We conducted a randomized, double-blind, placebo controlled study of basic

*Stimulus is
now b.v. growth
no substance*

JLin

the moment of injection. Serial ECGs showed no evidence of new **myocardial** infarction in any patient. Intraoperative blood loss was 0 to 50 cm³, and total chest tube drainage was 110 to 395 cm³. Postoperative **cardiac** output fell transiently but increased within 24 h (preanesthesia=4.8 vs. postanesthesia=4.1 vs. 24 h postoperative=6.3). Time to extubation after closure was 18.4 min; average postoperative hospital stay was 3.8 days. All patients had significant reduction in angina (nitroglycerin [NTG] use=53.9/wk pre-GTx vs. 9.8/wk post-GTx). Postoperative left ventricular ejection fraction (LVEF) was either unchanged or improved (mean increase in LVEF=5%). Objective evidence of reduced **ischemia** was documented using dobutamine single photon emission computed tomog. (SPECT)-sestamibi **imaging** in all patients. Coronary angiog. showed improved Rentrop score in 5 of 5 patients. This initial experience with naked gene transfer as sole therapy for **myocardial ischemia** suggests that direct **myocardial** injection of naked plasmid DNA, via a minimally invasive chest wall incision, is safe and may lead to reduced symptoms and improved **myocardial perfusion** in selected patients with chronic **myocardial ischemia**.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1998:93637 HCAPLUS

DOCUMENT NUMBER: 128:213011

TITLE: Biologic bypass with the use of adenovirus-mediated gene transfer of the complementary deoxyribonucleic acid for vascular endothelial growth factor 121 improves **myocardial perfusion** and function in the **ischemic porcine heart**

AUTHOR(S): Mack, Charles A.; Patel, Shailen R.; Schwarz, Eric A.; Zanzonico, Pat; Hahn, Rebecca T.; Ilercil, Arzu; Devereux, Richard B.; Goldsmith, Stanley J.; Christian, Timothy F.; Sanborn, Timothy A.; Kovesdi, Imre; Hackett, Neil; Isom, O. Wayne; Crystal, Ronald G.; Rosengart, Todd K.

CORPORATE SOURCE: Department of Cardiothoracic Surgery, The New York Hospital-Cornell Medical Center, New York, NY, 10021, USA

SOURCE: Journal of Thoracic and Cardiovascular Surgery (1998), 115(1), 168-177

CODEN: JTCSAQ; ISSN: 0022-5223

PUBLISHER: Mosby-Year Book, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Vascular endothelial growth factor (VEGF), a potent angiogenic mediator, can be delivered to targeted tissues by means of a replication-deficient adenovirus (Ad) vector. We hypothesized that direct administration of Ad vector expressing the VEGF121 complementary DNA (AdGVVEGF121.10) into regions of **ischemic myocardium** would enhance collateral vessel formation and improve regional **perfusion** and function. Yorkshire swine underwent thoracotomy and placement of an Ameroid constrictor (Research Instruments & MFG, Corvallis, Ore.) on the circumflex coronary artery. Three weeks later, **myocardial perfusion** and function were assessed by single photon emission computed tomog. **imaging** (SPECT) with 99mTc-labeled sestamibi and by echocardiog. during rest and stress. AdGVVEGF121.10 (n = 7) or the control vector, AdNull (n = 8), was administered directly into

growth factor improves function in ischemic heart

20/3,KWIC/2 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

07200537 Genuine Article#: 135PB No. References: 31

Title: VEGF administration in chronic myocardial ischemia in pigs
Author(s): Lopez JJ; Laham RJ; Stamler A; Pearlman JD; Bunting S; Kaplan A;
Carrozza JP; Sellke FW; Simons M (REPRINT)
Corporate Source: BETH ISRAEL DEACONESS MED CTR, ANGIOGENESIS RES
CTR/BOSTON//MA/02215 (REPRINT); BETH ISRAEL DEACONESS MED
CTR, ANGIOGENESIS RES CTR/BOSTON//MA/02215; HARVARD UNIV, SCH
MED/BOSTON//MA/; BETH ISRAEL DEACONESS MED CTR, DIV
CARDIOVASC/BOSTON//MA/; BETH ISRAEL DEACONESS MED CTR, DEPT
SURG/BOSTON//MA/; BETH ISRAEL DEACONESS MED CTR, DEPT RADIOL/BOSTON//MA/
; LOCAL MED, /PALO ALTO//CA/; GENENTECH INC, /S SAN FRANCISCO//CA/94080
Journal: CARDIOVASCULAR RESEARCH, 1998, V40, N2 (NOV), P272-281
ISSN: 0008-6363 Publication date: 19981100
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

Title: VEGF administration in chronic myocardial ischemia in pigs
, 1998

Abstract: Objective: Previous investigations have shown the effectiveness of sustained intra- or extravascular administration of vascular endothelial growth factor (VEGF) in chronic **myocardial ischemia** in improvement of left ventricular function. The present investigations were undertaken in order to evaluate efficacy of a single bolus or local intracoronary delivery. Methods...

...received intracoronary administration of saline and served as a control (n = 9). Three weeks after initiation of therapy, the animals were evaluated with regard to **myocardial** perfusion and global as well as regional ventricular function. Results: All three VEGF treatment groups but not the control animals demonstrated a significant increase in the left-to-left (but not right-to-left) collateral index, **myocardial** blood flow (pre-therapy LCX vs. LAD (average of all groups): 0.76 +/- 0.35 vs. 0.96 +/- 0.38 ml*min(-1)*g(-1)...

...control animals (21 +/- 3.3 vs. 27 +/- 5.8, p = NS). Conclusion: Single intracoronary delivery (intravascular bolus or local delivery) of VEGF is effective in **stimulating** physiologically significant **angiogenesis** in porcine model of chronic **myocardial ischemia**. (C) 1998 Elsevier Science B.V. All rights reserved.

...Identifiers--FIBROBLAST GROWTH-FACTOR; CORONARY COLLATERAL DEVELOPMENT; ARTERY OCCLUSION; BLOOD-FLOW; THERAPEUTIC **ANGIOGENESIS**; PORCINE **HEARTS**; LIMB **ISCHEMIA**; RABBIT MODEL; DISEASE

*VEGF -
enhancing
arteries
myocardial
ischemia*

20/3,KWIC/3 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

06691412 Genuine Article#: ZK771 No. References: 66

Title: Arterial gene transfer of naked DNA for therapeutic angiogenesis : early clinical results

Author(s): Isner JM (REPRINT)
Corporate Source: TUFTS UNIV, SCH MED, DEPT MED/BOSTON//MA/02135 (REPRINT);
TUFTS UNIV, SCH MED, DEPT BIOMED RES/BOSTON//MA/02135; TUFTS UNIV, SCH
MED, DEPT RADIOL/BOSTON//MA/02135; TUFTS UNIV, SCH MED, ST ELIZABETHS
MED CTR, DEPT SURG/BOSTON//MA/02135

11/3,KWIC/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0013121573 BIOSIS NO.: 200100293412

Alleviation of myocardial ischemia after Kawasaki disease by heparin and exercise therapy

AUTHOR: Tateno Shigeru; Terai Masaru (Reprint); Niwa Koichiro; Jibiki Toshiaki; Hamada Hiromichi; Yasukawa Kumi; Honda Takafumi; Oana Shinji; Kohno Yoichi

AUTHOR ADDRESS: Department of Pediatrics, Chiba University School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba-shi, Chiba, 260-8670, Japan** Japan

JOURNAL: Circulation 103 (21): p2591-2597 May 29, 2001 2001

MEDIUM: print

ISSN: 0009-7322

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Background: Heparin **promotes angiogenesis**. We evaluated the effects of combined treatment with heparin and **exercise** on myocardial ischemia in the chronic stage of Kawasaki disease. Methods and Results: This study was conducted in 7 patients (aged 6 to 19 years) who had a totally occluded coronary artery and stress-induced myocardial ischemia in the collateral-dependent areas. Twice-daily **exercise** using a bicycle ergometer was performed with increments of 0.5 W/kg every 3 minutes up to maximal exertion for 10 days. Heparin, which immediately increased circulating hepatocyte growth factor, was given intravenously 10 minutes before each **exercise** period. Newly developed myocardial infarction, ventricular tachyarrhythmia, anginal attack, or hemorrhagic complication was not observed in any patient. Dipyridamole-loading single photon emission computed tomography documented improved myocardial **perfusion** in the collateral-dependent areas and a significant reduction in total defect scores in all patients after the completion of 20 sessions (P=0.01). In control patients who did not receive the heparin- **exercise** therapy, however, stress defect scores remained unchanged (n=1) or increased (n=2) during follow-up. Computerized quantitative coronary angiography provided evidence that the heparin- **exercise** therapy increased the diameter of the occluded artery to which collaterals terminated (P=0.001) but not that of the reference artery with which collaterals were not connected (P=0.96). Conclusions: The findings suggest that a series of heparin and **exercise** treatments over 10 days may have a dramatic effect on the alleviation of myocardial ischemia in collateral-dependent regions. This may be a safe, noninvasive...

? t s11/3,kwic/2-10

Hep +
Exercise
Bicycle
Sildenafil?

11/3,KWIC/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

0011650242 BIOSIS NO.: 199800444489

Exercise training in swine promotes growth of arteriolar bed and capillary angiogenesis in heart

AUTHOR: White Francis C; Bloor Colin M; McKirnan M Dan; Carroll Susan M (Reprint)

AUTHOR ADDRESS: Univ. California San Diego Sch. Med., 9500 Gilman Dr., La Jolla, CA 92093-0612, USA**USA

JOURNAL: Journal of Applied Physiology 85 (3): p1160-1168 Sept., 1998 1998

MEDIUM: print

ISSN: 8750-7587
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

Exercise training in swine promotes growth of arteriolar bed and capillary angiogenesis in heart

ABSTRACT: **Exercise** training induces coronary vascular adaptations. The goal of this study was to contrast the effects of training on capillary and arteriolar growth. Minipigs were trained...
...Maximal O₂ consumption increased continuously throughout the study. Capillary and arteriolar densities and diameters, and proliferation of vascular cells in these vessels, were determined in **perfusion**-fixed tissue. The arterioles were subdivided into five groups according to diameter: 10-19.9, 20-30, 31-40, 41-70, and 71-120 μ m...

DESCRIPTORS:

MISCELLANEOUS TERMS: capillary **angiogenesis** ;

11/3,KWIC/3 (Item 3 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

0010817341 BIOSIS NO.: 199799451401

Basic fibroblast growth factor as a biochemical marker of exercise-induced ischemia

AUTHOR: Gu Jian-Wei; Santiago Derek; Olowe Yetunde; Weinberger Judah
(Reprint)

AUTHOR ADDRESS: Columbia-Presbyterian Hosp., 161 Fort Washington Ave., New York, NY 10032, USA**USA

JOURNAL: Circulation 95 (5): p1165-1168 1997 1997

ISSN: 0009-7322

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

...ABSTRACT: with metastatic tumors, but its expression in human myocardial ischemia is unknown. Thus, we sought to determine whether urine levels of bFGF are altered by **exercise**-induced ischemia in humans. Methods and Results. Eighty-six patients underwent **exercise** thallium studies for evaluation of anginal symptoms. Urine levels of bFGF (corrected for urine creatinine) were determined by ELISA immediately before and between 2 and 4 hours after **exercise**. The change in urine bFGF level was compared between 43 patients with and 43 patients without **exercise**-induced ischemia. Patients with ischemia had an increase in urine bFGF compared with nonischemic patients (1052 \pm 245 versus -278 \pm 130 pg/g creatinine, P lt .0001). **Exercise**, demographic, and clinical variables were assessed and analyzed for possible effect on bFGF response to **exercise**. By univariate analysis, a history of hypertension was negatively associated with a change in bFGF level (P lt .05). No other variables were associated. By multivariate analysis, only bFGF response (P lt .001) and age (P lt .05) were independently related to **exercise**-induced ischemia. Conclusions. Significantly increased levels of bFGF are detected in the urine within hours of **exercise**-induced ischemia. Further studies are warranted to determine whether bFGF might serve as a useful circulating marker of myocardial ischemia in humans.

11/3,KWIC/4 (Item 4 from file: 5)

Title: EFFECT OF CORONARY COLLATERAL CIRCULATION ON MYOCARDIAL-ISCHEMIA AND VENTRICULAR DYSFUNCTION

Author(s): SASAYAMA S

Corporate Source: KYOTO UNIV, DEPT INTERNAL MED, DIV 3, SAKYO KU, 54
KAWARACHO, SHOGGIN/KYOTO 606//JAPAN/

Journal: CARDIOVASCULAR DRUGS AND THERAPY, 1994, V8, S2 (MAY), P327-334

ISSN: 0920-3206

Language: ENGLISH Document Type: ARTICLE (Abstract Available)

...Abstract: observed the following facts in our studies during intracoronary thrombolytic therapy: (a) Myocardial ischemia is important for the development of collateral circulation, (b) collaterals can **perfuse** the infarcted myocardium, and (c) the presence of collaterals prevents the left ventricular aneurysm formation in acute myocardial infarction, even when the amount of the ...

...merely markers of severe ischemia but help to preserve the functional integrity of the myocardium in the presence of coronary obstruction. We then attempted to **promote** collateralization to treat patients with angina pectoris. Patients with chronic stable effort angina were treated with heparin followed by treadmill **exercise** twice a day for 10 days. Treadmill capacity was found to improve in association with an increase in coronary collateral circulation. Heparin treatment of ischemic...

...Identifiers--TREADMILL CAPACITY; ANEURYSM FORMATION; ARTERY OCCLUSION; EFFORT ANGINA; INFARCTION; HEPARIN; FLOW; **ANGIOGENESIS**; ANASTOMOSES; REPERFUSION

11/3, KWIC/7 (Item 3 from file: 34)

DIALOG(R) File 34: SciSearch(R) Cited Ref Sci

(c) 2003 Inst for Sci Info. All rts. reserv.

03337293 Genuine Article#: NW496 No. References: 49

Title: BIPHASIC INDUCTION OF IMMEDIATE-EARLY GENE-EXPRESSION ACCOMPANIES ACTIVITY-DEPENDENT ANGIOGENESIS AND MYOFIBER REMODELING OF RABBIT SKELETAL-MUSCLE

Author(s): MICHEL JB; ORDWAY GA; RICHARDSON JA; WILLIAMS RS

Corporate Source: UNIV TEXAS, SW MED CTR, RYBURN CTR MOLEC CARDIOL, DEPT
INTERNAL MED, NB 11200, 5323 HARRY HINES BLVD/DALLAS//TX/75235; UNIV
TEXAS, SW MED CTR, RYBURN CTR MOLEC CARDIOL, DEPT INTERNAL
MED/DALLAS//TX/75235; UNIV TEXAS, SW MED CTR, DEPT
BIOCHEM/DALLAS//TX/75235; UNIV TEXAS, SW MED CTR, DEPT
PHYSIOL/DALLAS//TX/75235; UNIV TEXAS, SW MED CTR, DEPT
PATHOL/DALLAS//TX/75235

Journal: JOURNAL OF CLINICAL INVESTIGATION, 1994, V94, N1 (JUL), P277-285

ISSN: 0021-9738

Language: ENGLISH Document Type: ARTICLE (Abstract Available)

Title: BIPHASIC INDUCTION OF IMMEDIATE-EARLY GENE-EXPRESSION ACCOMPANIES ACTIVITY-DEPENDENT ANGIOGENESIS AND MYOFIBER REMODELING OF RABBIT SKELETAL-MUSCLE

Abstract: Sustained contractile activity of skeletal muscle **promotes angiogenesis**, as well as transformation of contractile protein isoforms and mitochondrial proliferation within myofibers. Since the products of immediate early genes such as c-fos, c...

...Research Fronts: 002 (C-FOS INDUCTION; EXPRESSION OF GENES ENCODING TRANSCRIPTION FACTORS; RAT SUPRACHIASMATIC NUCLEUS CELLS; CORTICAL STIMULATION; STRIATAL NEURONS)

Exercise
Hep

Angiogenic gene therapy for stable angina is aimed at **promoting** new blood vessel formation in the heart, thus providing enhanced cardiac **perfusion**, symptom relief, increased **exercise** capacity, improved quality of life, and reduced risk of coronary events. Ad5FGF-4 is a replication-deficient serotype 5 adenovirus encoding the gene for fibroblast growth factor-4 (FGF-4) driven by a cytomegalovirus **promoter**. In preclinical studies using a pig model of myocardial ischemia, a single intracoronary infusion of Ad5FGF-4 improved cardiac contractile function and regional blood flow in the ischemic region during stress. These effects were apparent after 2 weeks and maintained for > or =12 weeks. Histologic evidence of capillary **angiogenesis** was observed. FGF-4 gene expression was detected in the heart but not at extracardiac sites. Placebo-controlled trials in humans with chronic stable angina indicate that Ad5FGF-4 increases treadmill **exercise** duration and improves stress-related ischemia measured by **perfusion** sestamibi single-photon emission computed tomography. More patients receiving Ad5FGF-4 than placebo reported complete resolution of their angina and no nitroglycerin use. Ad5FGF-4...

?

Control Factors Promoting perfusion, ischemic not part of treatment

provide serial assessment of ongoing vessel growth in vivo. Nuclear **imaging** (SPECT, PET) and x-ray angiog. have been used to assess changes in **perfusion** and anat. appearance, resp., after induced neovascular development. New **MRI** techniques provide the ability to identify early changes in vivo that are more sensitive to detection of the effects of new vessel growth than x-ray angiog. or nuclear **imaging**. These new **MRI** techniques include measurement of blood delivery to the **myocardium**, development of intramyocardial vasculature, and incremental changes in regional **myocardial** contractile function. With the combination of methods now available, we expect to be able to track key steps of **angiogenesis** in vivo and to assess the efficacy of angiogenic therapies. These new **imaging** capabilities offer crucial information which we hope will hasten the identification and deployment of effective pharmaceutical therapies as an adjunct or alternative to invasive treatments of **ischemic** disease by targeted stimulation of **angiogenesis**, and of cancer, by targeted inhibition of **angiogenesis**.

REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2001:894999 HCAPLUS

DOCUMENT NUMBER: 137:72895

TITLE: Effects of intramyocardial injection of phVEGF-A165 as sole therapy in patients with refractory coronary artery disease - 12-month follow-up: Angiogenic gene therapy

AUTHOR(S): Sarkar, N.; Ruck, A.; Kallner, G.; Y-Hassan, S.; Blomberg, P.; Islam, K. B.; Van Der Linden, J.; Lindblom, D.; Nygren, A. T.; Lind, B.; Brodin, L.-A.; Drvota, V.; Sylven, C.

CORPORATE SOURCE: Departments of Cardiology, Huddinge University Hospital, Stockholm, Swed.

SOURCE: Journal of Internal Medicine (2001), 250(5), 373-381
CODEN: JINMEO; ISSN: 0954-6820

PUBLISHER: Blackwell Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Objective. The objective was to test the safety and bioactivity of phVEGF-A165 after intramyocardial injection during 12-mo follow-up. Inclusion criteria were angina pectoris, Canadian Cardiovascular Society (CCS) class III-IV, unamenable to further revascularization, ejection fraction (EF) >30%, **perfusion** defects extending over >10% of the anterolateral left ventricle wall detectable with adenosine single photon emission computerized tomog. (SPECT) and at least one patent vessel visible by coronary angiog. Seven of 39 patients referred for gene therapy were included. Via a mini-thoracotomy under general anesthesia, phVEGF-A165 was injected directly into the **myocardium** at four sites in the anterolateral region of the left ventricle. Operative procedures were uneventful. Perioperative release of **myocardial** markers and ECG changes were detected in two patients. There were no perioperative deaths but one patient died 7 mo postoperatively because of **myocardial** infarction. Plasma vascular endothelial growth factor (VEGF)-A levels increased two to threefold peaking 6 days postoperatively ($P < 0.004$) and returning to baseline by day 30. A significant reduction in angina pectoris was reported. The CCS class improved from 3.3 ± 0.2 to 1.9 ± 0.3 ($P < 0.01$) and nitroglycerin intake decreased from 39 ± 15 to 12 ± 5 tablets week⁻¹ ($P < 0.001$) 2 mo after gene transfer. Improvements

JLin

remained after 12 mo when nitroglycerin consumption approached zero. Improved **myocardial** function in the phVEGF-A165 injection region was documented in all patients ($P < 0.016$) by tissue velocity **imaging** (TVI). Reduced reversible **ischemia** was detected by adenosine **SPECT** in four patients. Improved collateralization was detected in four patients with coronary angiog. Conclusion. Intramyocardial injection of phVEGF-A165 is safe and may lead to improved **myocardial perfusion** and function with longstanding symptomatic relief in end-stage angina pectoris. Based on these results this therapeutic potential is being tested in a double-blind placebo controlled multicenter trial.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2001:644118 HCAPLUS

DOCUMENT NUMBER: 136:64564

TITLE: Therapeutic **angiogenesis** with the use of vascular endothelial growth factor 165 gene in the **myocardium** of miniature swine

AUTHOR(S): Zhang, Duanzhen; Gai, Luyue; Chen, Yiwang; Fan, Ruiyun; Wen, Yingfeng; Dong, Wei

CORPORATE SOURCE: Department of Cardiology, the Chinese PLA General Hospital, Beijing, 100853, Peop. Rep. China

SOURCE: Shengli Xuebao (2001), 53(3), 183-187

CODEN: SLHPAH; ISSN: 0371-0874

PUBLISHER: Kexue Chubanshe

DOCUMENT TYPE: Journal

LANGUAGE: Chinese

AB Effects of adenovirus-mediated VEGF 165 (VEGF165) on collateral vessel formation of coronary artery and improve regional **myocardial perfusion** and function were studied in a miniature swine model of chronic **myocardial ischemia**. Th recombinant adenovirus vector containing complementary DNA (cdNA) for human VEGF165 (Ad-VEGF165) or for β -galactosidase (Ad -Gal) was administered directly into the **ischemic myocardium** in the left circumflex (LCX) distribution. **Myocardial perfusion** and function were assessed by ECG -gated single photon emission computed tomog. **imaging** and collateral vessel development of coronary artery was assessed by ex vivo coronary angiog. (CAG). 4 Wk after Ad-VEGF165 administration, **SPECT imaging** demonstrated a significant reduction in **ischemic area** and **ischemic severity**, and a substantial improvement in left ventricular ejection fraction and regional wall motion in the LCX distribution, as compared with those of control animals and those before administration of Ad-VEGF165. Collateral vessel development with Rentrop Grading was also significantly greater in Ad-VEGF165 animals than that in the Ad-Gal control animals. It shows that Ad-VEGF165 can induce collateral vessel development in **ischemic myocardium** and result in significant improvement in **myocardial perfusion** and function.

L17 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2000:475502 HCAPLUS

DOCUMENT NUMBER: 133:94539

TITLE: Composition and formulations and their use as nociceptic, anti-anxiolytic and anabolic agents

INVENTOR(S): Nyce, Jonathan W.

PATENT ASSIGNEE(S): USA

JLin

SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000040172	A1	20000713	WO 2000-US180	20000105
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2356368	AA	20000713	CA 2000-2356368	20000105
EP 1139913	A1	20011010	EP 2000-904212	20000105
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
BR 2000007397	A	20011030	BR 2000-7397	20000105
JP 2003523933	T2	20030812	JP 2000-591931	20000105
US 2003202935	A1	20031030	US 2000-554485	20000509
PRIORITY APPLN. INFO.:			US 1999-114773P	P 19990105
			WO 2000-US180	W 20000105

AB Composition and formulations comprising a first agent such as folinic acid, pharmaceutically acceptable salts thereof or mixts. thereof, and a second agent(s) such as analgesics, muscle relaxants, mood disorder agents, anti-inflammatories, anti-migraine agents, anti-emetics, diuretics, high protein composites, and the like are claimed. The products are suitable as nociceptics and for the treatment of wasting disorders, bulimia, anorexia nervosa, anxiety, irritability and other symptoms associated with premenstrual syndrome, as well as for administration either in conjunction with steroids or to compensate adenosine depletion and/or bizarre behavior or aggression common in steroid users. Administration of dehydroepiandrosterone (300 mg/kg) or methyltestosterone (40 mg/kg) daily to rats for 2 wk showed multi-organ depletion of adenosine. Co-administration of folinic acid completely abrogated adenosine depletion. Folinic acid administered alone induced increase in adenosine levels for all organs studied.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:81371 HCAPLUS
DOCUMENT NUMBER: 132:203377
TITLE: Intrapericardial delivery of fibroblast growth factor-2 induces neovascularization in a porcine model of chronic myocardial ischemia
AUTHOR(S): Laham, Roger J.; Rezaee, Mehrdad; Post, Mark; Novicki, Debborah; Sellke, Frank W.; Pearlman, Justin D.; Simons, Michael; Hung, David
CORPORATE SOURCE: Angiogenesis Research Center and Interventional Cardiology Section, Department of Medicine, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, MA, USA

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L17 ANSWER 1 OF 11 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2003:175034 HCAPLUS

DOCUMENT NUMBER: 139:63736

TITLE: The VIVA trial: vascular endothelial **growth factor** in **ischemia** for vascular **angiogenesis**

AUTHOR(S): Henry, Timothy D.; Annex, Brian H.; McKendall, George R.; Azrin, Michael A.; Lopez, John J.; Giordano, Frank J.; Shah, P. K.; Willerson, James T.; Benza, Raymond L.; Berman, Daniel S.; Gibson, C. Michael; Bajamonde, Alex; Rundle, Amy Chen; Fine, Jennifer; McCluskey, Edward R.

CORPORATE SOURCE: Div. Cardiol. at Hennepin County Med. Cent., University of Minnesota, Minneapolis, MN, 55407, USA

SOURCE: Circulation (2003), 107(10), 1359-1365

CODEN: CIRCAZ; ISSN: 0009-7322

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Recombinant human vascular endothelial **growth factor** protein (rhVEGF) **stimulates angiogenesis** in animal models and was well tolerated in Phase I clin. trials. VIVA (Vascular endothelial **growth factor** in **Ischemia** for Vascular **Angiogenesis**) is a double-blind, placebo-controlled trial designed to evaluate the safety and efficacy of intracoronary and i.v. infusions of rhVEGF. A total of 178 patients with stable exertional angina, unsuitable for standard revascularization, were randomized to receive placebo, low-dose rhVEGF (17 ng · kg⁻¹ · min⁻¹), or high-dose rhVEGF (50 ng · kg⁻¹ · min⁻¹) by intracoronary infusion on day 0, followed by i.v. infusions on days 3, 6, and exercise treadmill tests, angina class, and quality of life assessments were performed at baseline, day 60, and day 120. **Myocardial perfusion imaging** was performed at baseline and day 60. At day 60, the change in exercise treadmill test (ETT) time from baseline was not different between groups (placebo, +48 s; low dose, +30 s; high dose, +30 s). Angina class and quality of life were significantly improved within each group, with no difference between groups. By day 120, placebo-treated patients demonstrated reduced benefit in all three measures, with no significant difference compared with low-dose rhVEGF. In contrast, high-dose rhVEGF resulted in significant improvement in angina class (P=0.05) and nonsignificant trends in ETT time (P=0.15) and angina frequency (P=0.09) as compared with placebo. RhVEGF seems to be safe and well tolerated. RhVEGF offered no improvement beyond placebo in all measurements by day 60. By day 120, high-dose rhVEGF resulted in significant improvement in angina and favorable trends in ETT time and angina frequency.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2003:895952 HCAPLUS

TITLE: A randomized, double-blind, placebo-controlled trial of Ad5FGF-4 gene therapy and its effect on **myocardial perfusion** in patients with stable angina

AUTHOR(S): Grines, Cindy L.; Watkins, Matthew W.; Mahmarian, John J.; Iskandrian, Ami E.; Rade, Jeffrey J.; Marrott, Pran; Pratt, Craig; Kleiman, Neal

...Title Terms: **ANGIOGENESIS** ;

severity of the **perfusion** abnormalities was calculated by two blinded investigators. Compared to baseline, there was no significant change in exercise duration or peak rate-pressure product achieved with either placebo or adenosine plus heparin. In comparison there was a significant reduction in the severity of myocardial **perfusion** abnormalities in patients who received adenosine plus heparin. The results showed that repeated administrations of adenosine and heparin reduced the exercise-induced **ischemia** in patients with chronic stable angina refractory to conventional treatment. Administration is continuous for 6 minutes/day for a week or more (claimed). Hepa

14/3,KWIC/5 (Item 5 from file: 350)
DIALOG(R) File 350:Derwent WPIX
(c) 2003 Thomson Derwent. All rts. reserv.

012471095

WPI Acc No: 1999-277203/199923

XRAM Acc No: C99-081396

Treatment of occlusive peripheral vascular disease, coronary disease and associated disorders - comprises co-administration of adenosine A - 2 receptor agonist, e.g. adenosine, and heparin and/or a heparin-like substance in low, daily dosages for one week or more

Patent Assignee: UNIV CALIFORNIA (REGC)

Inventor: BARRON H V; BOTVINICK E

Number of Countries: 084 Number of Patents: 006

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
WO 9917784	A1	19990415	WO 98US21153	A	19981007	199923 B
AU 9897909	A	19990427	AU 9897909	A	19981007	199936
US 5972903	A	19991026	US 97946196	A	19971007	199952
EP 1021195	A1	20000726	EP 98952141	A	19981007	200037
			WO 98US21153	A	19981007	
US 6440947	B1	20020827	US 97946196	A	19971007	200259
			US 98167816	A	19981007	
JP 2003506310	W	20030218	WO 98US21153	A	19981007	200315
			JP 2000514655	A	19981007	

Priority Applications (No Type Date): US 98167816 A 19981007; US 97946196 A 19971007

Patent Details:

Patent No Kind Lan Pg Main IPC Filing Notes

WO 9917784 A1 E 46 A61K-031/715

Designated States (National): AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW

Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW

AU 9897909 A A61K-031/715 Based on patent WO 9917784

US 5972903 A A61K-031/70

EP 1021195 A1 E A61K-031/715 Based on patent WO 9917784

Designated States (Regional): AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

US 6440947 B1 A61K-031/70 CIP of application US 97946196

JP 2003506310 W 46 A61K-031/727 Based on patent WO 9917784

...Abstract (Basic): and heparin and/or a heparin-like substance is used to treat occlusive peripheral vascular disease, coronary disease and associated disorders and to promote coronary **angiogenesis** (claimed). The treatment is used to improve collateral coronary circulation in patients suffering from myocardial infarction to restore **cardiac** function after myocardial infarction and to improve blood flow in patients with coronary artery disease suffering from myocardial **ischemia** or inadequate blood flow to areas other than the **heart**, e.g. occlusive peripheral vascular disease, where decreased blood flow is a problem. Subjects with chronic, stable angina refractory to conventional medical therapy and unsuited...

...bolus; n=9) or placebo (n=6), daily for 10 days. All patients underwent baseline and follow-up exercise testing with Thallium 201 SPECT myocardial **perfusion imaging**. A semi-quantitative assessment of the

fibroblast growth factor (bFGF; 10 or 100µg vs. placebo) delivered via sustained-release heparin-alginate microcapsules implanted in **ischemic** and viable but ungraftable **myocardial** territories in patients undergoing CABG. Twenty-four patients were randomized to 10 µg of bFGF (n=8), 100 µg of bFGF (n=8), or placebo (n=8), in addition to undergoing CABG. There were 2 operative deaths and 3 Q-wave **myocardial** infarctions. There were no treatment-related adverse events, and there was no rise in serum bFGF levels. Clin. follow-up was available for all patients (16.0±6.8 mo). Three control patients had recurrent angina, 2 of whom required repeat revascularization. One patient in the 10-µg bFGF group had angina, whereas all patients in the 100-µg bFGF group remained angina-free. Stress nuclear **perfusion imaging** at baseline and 3 mo after CABG showed a trend toward worsening of the defect size in the placebo group (20.7±3.7% to 23.8±5.7%, P=0.06), no significant change in the 10-µg bFGF group, and significant improvement in the 100-µg bFGF group (19.2±5.0% to 9.1±5.9%, P=0.01). **Magnetic resonance** assessment of the target **ischemic** zone in a subset of patients showed a trend toward a reduction in the target **ischemic** area in the 100-µg bFGF group (10.7±3.9% to 3.7±6.3%, P=0.06). This study of bFGF in patients undergoing CABG demonstrates the safety and feasibility of this mode of therapy in patients with viable **myocardium** that cannot be adequately revascularized.

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1999:36422 HCAPLUS

DOCUMENT NUMBER: 130:261729

TITLE: Gene therapy for **myocardial angiogenesis** initial clinical results with direct **myocardial** injection of phVEGF165 as sole therapy for **myocardial ischemia**

AUTHOR(S): Losordo, Douglas W.; Vale, Peter R.; Symes, James F.; Dunnington, Cheryl H.; Esakof, Darryl D.; Maysky, Michael; Ashare, Alan B.; Lathi, Kishor; Isner, Jeffrey M.

CORPORATE SOURCE: Departments of Medicine, Biomedical Research, Surgery, and Anesthesiology, St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, MA, 02135, USA

SOURCE: Circulation (1998), 98(25), 2800-2804
CODEN: CIRCAZ; ISSN: 0009-7322

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors initiated a phase 1 clin. study to determine the safety and bioactivity of direct **myocardial** gene transfer of vascular endothelial growth factor (VEGF) as sole therapy for patients with symptomatic **myocardial ischemia**. VEGF gene transfer (GTx) was performed in 5 patients (all male, ages 53 to 71) who had failed conventional therapy; these men had angina (determined by angiog. documented coronary artery disease). Naked plasmid DNA encoding VEGF (phVEGF165) was injected directly into the **ischemic myocardium** via a mini left anterior thoracotomy. Injections caused no changes in **heart** rate (pre-GTx=75/min vs. post-GTx=80/min, P=NS), systolic BP (114 vs. 118 mm Hg, P=NS), or diastolic BP (57 vs. 59 mm Hg, P=NS). Ventricular arrhythmias were limited to single unifocal premature beats at

the **myocardium** at 10 sites in the circumflex distribution (108 pfu/site). Four weeks later, these studies were repeated and ex vivo angiog. was performed. **SPECT imaging** 4 wk after vector administration demonstrated significant reduction in the **ischemic** area at stress in AdGVVEGF121.10-treated animals compared with AdNull control animals ($p = 0.005$). Stress echocardiog. at the same time demonstrated improved segmental wall thickening in AdGVVEGF121.10 animals compared with AdNull control animals ($p = 0.03$), with AdGVVEGF121.10 animals showing nearly normalized function in the circumflex distribution. Collateral vessel development assessed by angiog. was also significantly greater in AdGVVEGF121.10 animals than in AdNull control animals ($p = 0.04$), with almost complete reconstitution of circumflex filling in AdGVVEGF121.10 animals. An Ad vector expressing the VEGF121 cDNA induces collateral vessel development in **ischemic myocardium** and results in significant improvement in both **myocardial perfusion** and function. Such a strategy may be useful in patients with **ischemic heart** disease in whom complete revascularization is not possible.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1995:845403 HCAPLUS

DOCUMENT NUMBER: 123:247600

TITLE: **Magnetic resonance** mapping demonstrates benefits of VEGF-induced **myocardial angiogenesis**

AUTHOR(S): Pearlman, Justin D.; Hibberd, Mark G.; Chuang, Michael L.; Harada, Kazumasa; Lopez, John J.; Gladstone, Stephen R.; Friedman, Menahem; Sellke, Frank W.; Simons, Michael

CORPORATE SOURCE: Department of Radiology, Harvard Medical School, Boston, MA, 02215, USA

SOURCE: Nature Medicine (New York) (1995), 1(10), 1085-9
CODEN: NAMEFI; ISSN: 1078-8956

PUBLISHER: Nature Publishing Co.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Coronary occlusive disease is the leading cause of death in industrial nations and affects one in 4 adults. Although **heart** attacks are caused by occlusion of a coronary artery, some patients have occlusions without infarction because they have sufficient collateral vessels providing an alternate pathway for blood supply. Vascular endothelial **growth factor** (VEGF) is an angiogenic peptide that can **stimulate** collateral vessel development in the **ischemic myocardium**. We used **magnetic resonance imaging** (MRI) and image processing to identify and quantify noninvasively the benefits related to VEGF infusion on collateral development in the **heart**. This was accomplished as a placebo-controlled study in the porcine model of chronic **ischemia** that most closely mimics the human pathophysiol. of progressive coronary occlusion. Image series converted to a space-time map demonstrated that with treatment the **ischemic** zone was smaller and the contrast arrival delay was less, which resulted in better ejection fraction and regional wall thickening. These findings demonstrate in a manner applicable to humans, that VEGF improves collateral blood supply, resulting in improved **cardiac** global and regional function after and in spite of coronary artery occlusion.

20/3,KWIC/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0011635360 BIOSIS NO.: 199800429607

Vascular endothelial growth factor-C (VEGF-C/VEGF-2) promotes angiogenesis in the setting of tissue ischemia

AUTHOR: Witzembichler Bernhard; Asahara Takayuki; Murohara Toyoaki; Silver Marcy; Spyridopoulos Ioakim; Magner Meredith; Principe Nicole; Kearney Marianne; Hu Jing-Shan; Isner Jeffrey M (Reprint)

AUTHOR ADDRESS: St. Elizabeth's Med. Cent. Boston, 736 Cambridge St., Boston, MA 02135, USA**USA

JOURNAL: American Journal of Pathology 153 (2): p381-394 Aug., 1998 1998

MEDIUM: print

ISSN: 0002-9440

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

Vascular endothelial growth factor-C (VEGF-C/VEGF-2) promotes angiogenesis in the setting of tissue ischemia
1998

...ABSTRACT: to development of the lymphatic vasculature. The current studies were designed to test the hypothesis that constitutive expression of VEGF-C in adult animals promotes **angiogenesis**. In vitro, VEGF-C exhibited a dose-dependent mitogenic and chemotactic effect on endothelial cells, particularly for microvascular endothelial cells (72% and 95% potency, respectively, compared with VEGF-A/VEGF-1). VEGF-C **stimulated** release of nitric oxide from endothelial cells and increased vascular permeability in the Miles assay; the latter effect was attenuated by pretreatment with the nitric...

...2 and VEGFR-3 receptors were shown to be expressed in human saphenous vein and internal mammary artery. The potential for VEGF-C to promote **angiogenesis** in vivo was then tested in a rabbit **ischemic** hindlimb model. Ten days after ligation of the external iliac artery, VEGF-C was administered as naked plasmid DNA (pcVEGF-C; 500 mug) from the...

...an angioplasty balloon (n=8 each) or as recombinant human protein (rhVEGF-C; 500 mug) by direct intra-arterial infusion. Physiological and anatomical assessments of **angiogenesis** 30 days later showed evidence of therapeutic **angiogenesis** for both pcVEGF-C and rhVEGF-C. Hindlimb blood pressure ratio (**ischemic** /normal) after pcVEGF-C increased to 0.83 +- 0.03 after pcVEGF-C versus 0.59 +- 0.04 (P < 0.005) in pGSVLacZ controls and...

...164 +- 20 (P < 0.05) for protein). in contrast to the results of gene targeting experiments, constitutive expression of VEGF-C in adult animals promotes **angiogenesis** in the setting of limb **ischemia**. VEGF-C and its receptors thus constitute an apparently redundant pathway for postnatal **angiogenesis** and may represent an alternative to VEGF-A for strategies of therapeutic **angiogenesis** in patients with limb and/or **myocardial ischemia**.

DESCRIPTORS:

DISEASES: **myocardial ischemia** -- heart disease, vascular disease

MESH TERMS: **Myocardial Ischemia** (MeSH...

...METHODS & EQUIPMENT: **imaging** method

MISCELLANEOUS TERMS: **angiogenesis** ;

Journal: ADVANCED DRUG DELIVERY REVIEWS, 1998 , V30, N1-3 (MAR 2), P 185-197
ISSN: 0169-409X Publication date: 19980302
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS
Language: English Document Type: REVIEW (ABSTRACT AVAILABLE)

Title: Arterial gene transfer of naked DNA for therapeutic angiogenesis : early clinical results
1998

Abstract: Patients with critical limb ischemia constitute a potential target population for therapeutic **angiogenesis** , Because the growth of new collateral vessels can be achieved in a time interval of 1 month or less, these patients are suitable candidates for...
...extremity. Using a dose-escalating strategy, it was possible to document that naked DNA was sufficient to generate evidence of new collateral growth by both **magnetic resonance** angiography and contrast angiography in the affected limb. These findings establish that the use of naked DNA may be suitable for gene therapy when the...
...Identifiers--ENDOTHELIAL GROWTH-FACTOR; IN-VIVO; PERCUTANEOUS REVASCULARIZATION; **ISCHEMIC MYOCARDIUM** ; PROTEIN SECRETION; EXPRESSION; BALLOON; **INJURY**; INVIVO; MODEL

20/3,KWIC/4 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

06653920 Genuine Article#: ZH422 No. References: 19

Title: Extent of myocardial collateralization: Determination with three-dimensional elastic-subtraction spiral CT

Author(s): Pearlman JD (REPRINT) ; Laham RJ; Simons M; Gladstone S; Raptopoulos V

Corporate Source: HARVARD UNIV,SCH MED, BETH ISRAEL DEACONESS MED CTR AN240, DEPT RADIOL, 330 BROOKLINE AV/BOSTON//MA/02215 (REPRINT); HARVARD UNIV,SCH MED, BETH ISRAEL DEACONESS MED CTR AN240, DEPT MED/BOSTON//MA/02215

Journal: ACADEMIC RADIOLOGY, 1997 , V4, N10 (OCT), P680-686

ISSN: 1076-6332 Publication date: 19971000

Publisher: ASSOC UNIV RADIOLOGISTS, 2021 SPRING RD, STE 600, OAK BROOK, IL 60521

Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

1997

Abstract: Rationale and objectives. This study was undertaken to develop a standard that can be used to assess new high-resolution collateral zone **imaging** methods.

Materials and Methods. The authors performed ex vivo helical CT in seven pig hearts after microsphere studies of blood flow and coronary angiography. They...

...was 6.5%, which indicates good agreement.

Conclusion. Accurate assessment of collateralization extent has become an important goal because of the discovery of agents that **stimulate** the growth of coronary collateral vessels. The precision of elastic-subtraction CT and its validation with respect to the blood flow distribution at microsphere analysis...

...Identifiers--FIBROBLAST GROWTH-FACTOR; BLOOD-FLOW; **ISCHEMIC MYOCARDIUM** ; CORONARY-OCCLUSION; **ANGIOGENESIS**; CIRCULATION;

INFARCTION; MODEL; DOG

20/3,KWIC/5 (Item 4 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

06263928 Genuine Article#: YF058 No. References: 58

Title: Protection of rat myocardium by mitogenic and non-mitogenic fibroblast growth factor during post- ischemic reperfusion

Author(s): Cuevas P; Carceller F; Lozano RM; Crespò A; Zazo M; GimenezGallego G (REPRINT)

Corporate Source: CSIC,CTR INVEST BIOL, VELAZQUEZ 144/E-28006 MADRID//SPAIN/ (REPRINT); CSIC,CTR INVEST BIOL/E-28006 MADRID//SPAIN/; UNIV MADRID,HOSP RAMON Y CAJAL/MADRID 3//SPAIN/

Journal: GROWTH FACTORS, 1997, V15, N1, P29-&

ISSN: 0897-7194 Publication date: 19970000

Publisher: HARWOOD ACAD PUBL GMBH, C/O STBS LTD, PO BOX 90, READING, BERKS, ENGLAND RG1 8JL

Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

Title: Protection of rat myocardium by mitogenic and non-mitogenic fibroblast growth factor during post- ischemic reperfusion, 1997

Abstract: The effects of acidic fibroblast growth factor (FGF-1) and basic fibroblast growth factor (FGF-2) and a non mitogenic form of FGF1 on **myocardial ischemia** and reperfusion were assessed. Rats underwent 10 minutes of coronary artery occlusion followed by 24 hours of reperfusion. Creatinine kinase content of the affected **myocardium** showed that both fibroblast growth factors 1 and 2 effectively protected against **ischemia reperfusion injury** ($p < 0.01$), and that the vasoactive but nonmitogenic form of the FGF1 was equally protective ($p < 0.01$ versus control + vehicle). The results were...

...form of the protein, also suggest that the protective effect of fibroblast growth factors may be due to the increased blood flow rather than to **angiogenesis**.

...Research Fronts: FACTOR BB; RESTENOSIS FOLLOWING CORONARY ANGIOPLASTY; RABBIT ARTERIES)

95-1848 001 (MYOCARDIAL VIABILITY; DOBUTAMINE STRESS ECHOCARDIOGRAPHY; CHRONIC CORONARY-ARTERY DISEASE; CLINICAL USE OF CARDIAC RADIONUCLIDE **IMAGING**)

95-8705 001 (**MYOCARDIAL REPERFUSION INJURY** ; ENDOTHELIAL NITRIC-OXIDE SYNTHASE; HYPOTHERMIC **ISCHEMIA** IN NEONATAL LAMB **HEARTS** ; CORONARY FLOW; L-ARGININE CARDIOPLEGIA)

20/3,KWIC/6 (Item 5 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

06016974 Genuine Article#: XP599 No. References: 109

Title: Role of cytokines in myocardial ischemia and reperfusion

Author(s): Sharma HS (REPRINT) ; Das DK

Corporate Source: ERASMUS UNIV ROTTERDAM,DEPT PHARMACOL/NL-3000 DR ROTTERDAM//NETHERLANDS/ (REPRINT); UNIV CONNECTICUT,CTR HLTH, DEPT SURG/FARMINGTON//CT/

Journal: MEDIATORS OF INFLAMMATION, 1997, V6, N3 (JUN), P175-183

ISSN: 0962-9351 Publication date: 19970600

Publisher: RAPID SCIENCE PUBLISHERS, 2-6 BOUNDARY ROW, LONDON, ENGLAND SE1

8NH

Language: English Document Type: REVIEW (ABSTRACT AVAILABLE)

Title: Role of cytokines in myocardial ischemia and reperfusion
, 1997

Abstract: Mediators of **myocardial** inflammation, predominantly cytokines, have for many years been implicated in the healing processes after infarction. In recent years, however, more attention has been paid to the possibility that the inflammation may result in deleterious complications for **myocardial** infarction. The proinflammatory cytokines may mediate **myocardial** dysfunction associated with **myocardial** infarction, severe congestive **heart** failure, and sepsis. A growing body of literature suggests that inflammatory mediators could play a crucial role in **ischemia** -reperfusion **injury**. Furthermore, **ischemia** -reperfusion not only results in the local transcriptional and translational upregulation of cytokines but also leads to tissue infiltration by inflammatory cells. These inflammatory cells...

...metabolism and subsequent irreversible cell membrane damage leading to cell death. For instance, hypoxic cardiomyocytes produce interleukin-6 (IL-6) which could contribute to the **myocardial** dysfunction observed in **ischemiareperfusion injury**. **Ischemia** followed by reperfusion induces a number of other multi-potent cytokines, such as IL-1, IL-8, tumor necrosis factor-alpha (TNF-alpha), transforming growth factor-alpha (TGF-beta 1) as well as an angiogenic cytokine/ growth factor, vascular endothelial growth factor (VEGF), in the **heart**. Interestingly, these multipotent cytokines (e.g. TNF-alpha) may induce an adaptive cytoprotective response in the reperfused **myocardium**. In this review, we have included a number of cytokines that may contribute to ventricular dysfunction and/or to the cytoprotective and adaptive changes in the reperfused **heart**.

...Research Fronts: POEMS SYNDROME; GIANT LYMPH-NODE HYPERPLASIA; MYELOMA CELLS)

95-1848 001 (MYOCARDIAL VIABILITY; DOBUTAMINE STRESS ECHOCARDIOGRAPHY; CHRONIC CORONARY-ARTERY DISEASE; CLINICAL USE OF CARDIAC RADIONUCLIDE **IMAGING**)

95-2892 001 (VASCULAR ENDOTHELIAL GROWTH-FACTOR; TUMOR **ANGIOGENESIS**; COORDINATE EXPRESSION)

95-3685 001 (CARDIOPULMONARY BYPASS; ARTIFICIAL SURFACES DEMONSTRATES REDUCED COMPLEMENT ACTIVATION; CIRCULATING ADHESION MOLECULES IN CARDIAC OPERATIONS)

95-7159 001 (HUMAN THYMIDINE KINASE...)

20/3,KWIC/7 (Item 6 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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05836444 Genuine Article#: XA653 No. References: 13

Title: Harmonic imaging of porcine intraovarian arteries using sonographic contrast medium initial findings

Author(s): Ragavendra N (REPRINT); Chen H; Powers JE; Nilawat C; Robert JM; Carangi C; LaiferNarin SL

Corporate Source: 300 UCLA MED PLAZA, SUITE 3102/LOS ANGELES//CA/90095 (REPRINT); UNIV CALIF LOS ANGELES, SCH MED, DEPT RADIOL SCI/LOS ANGELES//CA/90024

Journal: ULTRASOUND IN OBSTETRICS & GYNECOLOGY, 1997, V9, N4 (APR), P 266-270

ISSN: 0960-7692 **Publication date:** 19970400

Publisher: PARTHENON PUBLISHING GROUP, CASTERTON HALL, CARNFORTH

John Sims EIC 3700 308-4836

LANCASHIRE, ENGLAND LA6 2LA
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

Title: Harmonic imaging of porcine intraovarian arteries using sonographic contrast medium initial findings
1997

Abstract: The purpose of this study was to visualize, using harmonic gray-scale **imaging**, blood flow in porcine intraovarian arteries after intravenous injections of a bubble-based sonographic contrast medium. Five female pigs underwent laparotomy. Surgically isolated ovaries were scanned intraperitoneally by an ultrasound system reconfigured with software changes to accomplish harmonic **imaging**. The transmission and receiving frequencies were set at 3.75 and 7.5 MHz, respectively. After injection of the sonographic contrast medium (Aerosomes(R)) into a peripheral vein, the ovaries were imaged in the harmonic mode. Ten minutes later, another contrast injection was administered and conventional gray-scale **imaging** of the ovary performed. In all five pigs, intraovarian arteries were clearly identified upon harmonic **imaging** as brightly echogenic moving columns. The arterial blood pool appeared brighter during systole than diastole. Upon ultrasound contrast-assisted conventional gray-scale **imaging**, intraovarian arteries were not visualized in four pigs and poorly visualized in one. We conclude that contrast-assisted harmonic **imaging** can adequately visualize blood flow in intraovarian arteries of surgically exposed porcine ovaries. Clinically, harmonic **imaging** may facilitate early detection of tumor-induced **angiogenesis** in the human ovary.

Research Fronts: 95-5489 001 (**MYOCARDIAL CONTRAST ECHOCARDIOGRAPHY; ISCHEMIA -REPERFUSION INJURY** ; CANINE MODEL; CORONARY MICROCIRCULATION)

20/3,KWIC/8 (Item 7 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

05284259 Genuine Article#: VM749 No. References: 59

Title: GENE-TRANSFER OF NAKED DNA ENCODING FOR 3 ISOFORMS OF VASCULAR ENDOTHELIAL GROWTH-FACTOR STIMULATES COLLATERAL DEVELOPMENT IN-VIVO

Author(s): TAKESHITA S; TSURUMI Y; COUFFINAH T; ASAHARA T; BAUTERS C; SYMES J; FERRARA N; ISNER JM

Corporate Source: TUFTS UNIV,SCH MED,ST ELIZABETHS MED CTR,DEPT MED CARDIOL,736 CAMBRIDGE ST/BOSTON//MA/02135; TUFTS UNIV,SCH MED,ST ELIZABETHS MED CTR,DEPT MED CARDIOL/BOSTON//MA/02135; TUFTS UNIV,SCH MED,ST ELIZABETHS MED CTR,DEPT CARDIOVASC SURG/BOSTON//MA/02135; TUFTS UNIV,SCH MED,ST ELIZABETHS MED CTR,DEPT BIOMED RES/BOSTON//MA/02135; GENENTECH INC,DEPT CARDIOVASC RES/S SAN FRANCISCO//CA/94080

Journal: LABORATORY INVESTIGATION, 1996, V75, N4 (OCT), P487-501

ISSN: 0023-6837

Language: ENGLISH Document Type: ARTICLE (Abstract Available)

Title: GENE-TRANSFER OF NAKED DNA ENCODING FOR 3 ISOFORMS OF VASCULAR ENDOTHELIAL GROWTH-FACTOR STIMULATES COLLATERAL DEVELOPMENT IN-VIVO
1996

...**Abstract:** endothelial cell-specific mitogen. We investigated the hypothesis that naked DNA encoding for VEGF could be used in a strategy of arterial gene therapy to **stimulate** collateral artery development. Plasmid DNA encoding each of the three principal human VEGF isoforms (phVEGF(121), phVEGF(165), or phVEGF(189)) was applied to the...

...Similar results were obtained with phVEGF(121), phVEGF(165), and

phVEGF(189), which suggests that these isoforms are biologically equivalent with respect to in vivo **angiogenesis**. The fact that viral or other adjunctive vectors were not required further suggests that secreted gene products may have potential therapeutic utility even when the...

...cells remains low. Arterial gene transfer of naked DNA encoding for a secreted angiogenic cytokine, thus, represents a potential alternative to recombinant protein administration for **stimulating** collateral vessel development.

...Identifiers--IN-VIVO; THERAPEUTIC **ANGIOGENESIS**; CELLULAR PROLIFERATION; **ISCHEMIC MYOCARDIUM**; PROTEIN SECRETION; RABBIT MODEL; TIME-COURSE; EXPRESSION; INVIVO; ARTERY

Research Fronts: 94-5407 002 (VASCULAR ENDOTHELIAL GROWTH-FACTOR; CORONARY **ANGIOGENESIS**; WILD-TYPE P53 EXPRESSION IN GLIOBLASTOMA CELLS)

94-0253 001 (PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY; PROSPECTIVE RANDOMIZED TRIAL FOR ARTERIAL PUNCTURE SITE CLOSURE; PREDICTING ISCHEMIC COMPLICATIONS)

94-0785 001 (INTRAVASCULAR ULTRASOUND **IMAGING**; POSTSTENOTIC CORONARY FLOW RESERVE; UNSTABLE ANGINA)

94-8400 001 (DIRECT DNA INJECTION; VACCINE DELIVERY; IN-VIVO GENE-TRANSFER; PROTECTIVE IMMUNITY; NUCLEIC-ACID IMMUNIZATION; SKELETAL-MUSCLE...

20/3,KWIC/9 (Item 8 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

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03547673 Genuine Article#: PL936 No. References: 27

Title: SELECTIVE CLOSURE OF THE VASCULAR BED OF AN EXPERIMENTAL GLIOMA MODEL DURING IN-SITU SALINE PERFUSION

Author(s): LUTHERT PJ; GREENWOOD J

Corporate Source: INST OPHTHALMOL,DEPT PATHOL,BATH ST/LONDON

EC1V9EL//ENGLAND/; INST PSYCHIAT,DEPT NEUROPATHOL/LONDON SE5

8AF//ENGLAND/

Journal: NEUROPATHOLOGY AND APPLIED NEUROBIOLOGY, 1994, V20, N5 (OCT), P 448-453

ISSN: 0305-1846

Language: ENGLISH Document Type: ARTICLE (Abstract Available)

, 1994

...Identifiers--EXPERIMENTAL BRAIN-TUMORS; BLOOD-FLOW; RAT-BRAIN; PERMEABILITY; BARRIER; **ANGIOGENESIS**; CHEMOTHERAPY; TRANSPORT; TISSUE; LIGHT

Research Fronts: 92-0789 001 (**MYOCARDIAL REPERFUSION INJURY**; REACTIVE OXYGEN INTERMEDIATES; GASTRIC INTRAMUCOSAL PH; COLD **ISCHEMIA**)

92-2388 001 (**POSITRON EMISSION TOMOGRAPHY**; 3-DIMENSIONAL FUNCTIONAL BRAIN IMAGES; REGIONAL CEREBRAL BLOOD-FLOW)

92-5511 001 (TUMOR **ANGIOGENESIS**; FIBROBLAST GROWTH-FACTOR; ANTIANGIOGENIC AGENTS)

20/3,KWIC/10 (Item 1 from file: 73)

DIALOG(R)File 73:EMBASE

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06276632 EMBASE No: 1995302287

Magnetic resonance **mapping demonstrates benefits of VEGF-induced**

John Sims EIC 3700 308-4836

myocardial angiogenesis

Pearlman J.D.; Hibberd M.G.; Chuang M.L.; Harada K.; Lopez J.J.;
Gladstone S.R.; Friedman M.; Sellke F.W.; Simons M.
Department of Radiology, Harvard Medical School, Beth Israel
Hospital, Boston, MA 02215 United States
Nature Medicine (NAT. MED.) (United States) 1995, 1/10 (1085-1089)
CODEN: NAMEF ISSN: 1078-8956
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

**Magnetic resonance mapping demonstrates benefits of VEGF-induced
myocardial angiogenesis**

...infarction because they have sufficient collateral vessels providing
an alternate pathway for blood supply. Vascular endothelial growth factor
(VEGF) is an angiogenic peptide that can **stimulate** collateral vessel
development in the ischaemic myocardium. We used **magnetic resonance
imaging (MRI)** and image processing to identify and quantify
non-invasively the benefits related to VEGF infusion on collateral
development in the heart. This was accomplished as...

MEDICAL DESCRIPTORS:

* **angiogenesis** ; *coronary artery collateral circulation; *heart infarction
--prevention--pc; *heart infarction--drug therapy--dt; * **heart** muscle
ischemia

animal experiment; animal model; article; controlled study; intracardiac
drug administration; nonhuman; nuclear **magnetic resonance imaging** ;
priority journal; swine

1995

?

DIALOG(R)File 5:Biosis Previews(R)
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0006211583 BIOSIS NO.: 198886051504

IMPROVEMENT OF TREADMILL CAPACITY AND COLLATERAL CIRCULATION AS A RESULT OF EXERCISE WITH HEPARIN PRETREATMENT IN PATIENTS WITH EFFORT ANGINA

AUTHOR: FJUITA M (Reprint); SASAYAMA S; ASANOI H; NAKAJIMA H; SAKAI O; OHNO A

AUTHOR ADDRESS: SECOND DEP INTERNAL MED, TOYAMA MED PHARM UNIV, 2630 SUGITANI, TOYAMA 930-01, JPN**JAPAN

JOURNAL: Circulation 77 (5): p1022-1029 1988

ISSN: 0009-7322

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: ENGLISH

...ABSTRACT: the above-mentioned variables of treadmill capacity remained unchanged, despite 20 exercise periods without heparin pretreatment. Thus, heparin accelerates exercise-induced coronary collateral development by **promoting angiogenesis**. The development of such a therapeutic modality will open a new field for the treatment of patients with ischemia.

11/3,KWIC/5 (Item 1 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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03543731 Genuine Article#: PL505 No. References: 81

Title: CLINICAL-SIGNIFICANCE OF CORONARY VASCULAR ADAPTATIONS TO EXERCISE TRAINING

Author(s): MCKIRNAN MD; BLOOR CM

Corporate Source: UNIV CALIF SAN DIEGO, SCH MED, DEPT PATHOL, 0612, 9500 GILMAN DR/LA JOLLA//CA/92093; UNIV CALIF SAN DIEGO, SCH MED, DEPT PATHOL/LA JOLLA//CA/92093

Journal: MEDICINE AND SCIENCE IN SPORTS AND EXERCISE, 1994, V26, N10 (OCT), P1262-1268

ISSN: 0195-9131

Language: ENGLISH Document Type: ARTICLE (Abstract Available)

...Abstract: ischemia and measuring myocardial blood flow and the variability in exercise stimulus. Well-established ischemia and high-intensity, long-duration training were the factors that **promoted** vascular growth in exercising patients with coronary artery disease. Animals studies also have demonstrated the necessity for myocardial ischemia to be present to induce coronary collateral development with exercise training. Optimal **promoters** of vascular growth in patients with coronary disease may consist of pharmacological interventions combined with exercise training.

...Identifiers--LEFT-VENTRICULAR FUNCTION; HIGH-INTENSITY EXERCISE ; COLLATERAL BLOOD-FLOW; ARTERY DISEASE; MYOCARDIAL PERFUSION ; HEART-DISEASE; ANGINA-PECTORIS; PHYSICAL-ACTIVITY; CARDIAC REHABILITATION; PLASMA CATECHOLAMINES

11/3,KWIC/6 (Item 2 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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03396344 Genuine Article#: PB893 No. References: 31

92-2715 001 (INSULIN SENSITIVITY IN MUSCLE; **PERFUSIVE** O2 TRANSPORT
DURING **EXERCISE** ; DIAPHRAGMATIC FIBERS)

11/3,KWIC/8 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
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12114745 EMBASE No: 2003227993

Enhanced external counterpulsation for ischemic heart disease: What's behind the curtain?

Bonetti P.O.; Holmes Jr. D.R.; Lerman A.; Barsness G.W.
Dr. G.W. Barsness, Division of Cardiovascular Diseases, Mayo Clinic, 200
First Street SW, Rochester, MN 55905 United States
AUTHOR EMAIL: barsness.gregory@mayo.edu
Journal of the American College of Cardiology (J. AM. COLL. CARDIOL.) (United States) 04 JUN 2003, 41/11 (1918-1925)
CODEN: JACCD ISSN: 0735-1097
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 66

...patients with refractory angina. Prospective clinical studies and large treatment registries suggest that a course of EECP is associated with prolongation of the time to **exercise** -induced ST-segment depression and resolution of myocardial **perfusion** defects, as well as with enhanced **exercise** tolerance and quality of life. With a growing knowledge base supporting the safety and beneficial clinical effects associated with EECP, this therapy can be considered...

...the mechanisms responsible for the beneficial effects associated with this technique. Suggested mechanisms contributing to the clinical benefit of EECP include improvement in endothelial function, **promotion** of coronary collateralization, enhancement of ventricular function, peripheral effects similar to those observed with regular physical **exercise** , and nonspecific placebo effects. This review summarizes the current evidence for a contribution of these mechanisms to the clinical benefit associated with EECP. (c) 2003...

MEDICAL DESCRIPTORS:

...perfusion; stable angina pectoris--therapy--th; cardiovascular risk; oxidative stress; coronary artery dilatation; coronary artery blood flow; collateral circulation; peripheral circulation; protein induction; protein function; **angiogenesis** ; coronary artery collateral circulation; heart left ventricle function; exercise test; positron emission tomography; validation process; outcomes research; human; review; priority journal

11/3,KWIC/9 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE
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Therapeutic angiogenesis in critical limb and myocardial ischemia

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